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CANADIAN THESES ON MICROFICHE | THÈSES CANADIENNES SUR MICROFICHE

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TITLE OF THESIS/*TITRE DE LA THÈSE* Hemodynamic effects of exercise and training in angina patients

UNIVERSITY/*UNIVERSITÉ* University of Alberta

DEGREE FOR WHICH THESIS WAS PRESENTED/ *GRADE POUR LEQUEL CETTE THÈSE FUT PRÉSENTÉE* PhD

YEAR THIS DEGREE CONFERRED/*ANNÉE D'OBTENTION DE CE GRADE* ~~1978~~ 1978

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HEMODYNAMIC EFFECTS OF EXERCISE AND TRAINING IN ANGINA PATIENTS

by

© PIERRE GAUTHIER

A THESIS

SUBMITTED TO THE FACULTY OF GRADUATE STUDIES AND RESEARCH

IN PARTIAL FULFILMENT OF THE REQUIREMENTS FOR THE DEGREE

OF DOCTOR OF PHILOSOPHY

FACULTY OF PHYSICAL EDUCATION

EDMONTON, ALBERTA

SPRING, 1978

THE UNIVERSITY OF ALBERTA

FACULTY OF GRADUATE STUDIES AND RESEARCH

The undersigned certify that they have read, and recommend to the Faculty of Graduate Studies and Research, for acceptance, a thesis entitled "Hemodynamic Effects of Exercise and Training in Angina Patients", submitted by Pierre Gauthier in partial fulfilment of the requirements for the degree of Doctor of Philosophy in Physical Education.

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A mon épouse Dianne pour son soutien inconditionnel; qu'elle partage ma joie au moment de toucher au but.

ABSTRACT

This study evaluated the effects of four to six months bicycle ergometer training on coronary sinus blood flow (CSBF) and myocardial oxygen consumption ($M\dot{V}O_2$) in 11 patients with exertional angina pectoris and angiographically documented coronary artery disease. CSBF was determined by thermodilution before and after training, with the patient in the upright position under the following conditions: at rest, during exercise at an equivalent workload, during exercise at an equivalent heart rate and at symptom-limited exercise. Although resting heart rate was significantly lower (78±9 *vs* 70±5 beats/min) after training, CSBF, $M\dot{V}O_2$ and the product ($\overline{PRP}$) of mean brachial artery pressure times heart rate were unchanged. At an equivalent workload averaging 400 kgm/min heart rate (120±14 *vs* 103±11 beats/min), CSBF (163±36 *vs* 138±21 ml/min) and $\overline{PRP} \times 10^{-3}$ (15.2±27 *vs* 12.3±2.6) were significantly lower after training. $M\dot{V}O_2$ tended to be lower (20.1±5.2 *vs* 17.3±3.6 ml/min) but the difference was not significant ($p<0.10$). Arterial lactate and catecholamine concentrations were significantly lowered after training at this given workload. After training, patients could perform an 18% greater workload for a similar heart rate (mean 114 beats/min). CSBF, $M\dot{V}O_2$ and $\overline{PRP}$ were not significantly different despite this increase in absolute workload. However arterial lactate concentration was significantly lower after training (31.4±16.8 *vs* 24.0±13.9 mg%). Symptom-limited exercise capacity increased 38% with training. Maximal values for CSBF (195±52 *vs* 205±49 ml/min),

$M\dot{V}O_2$ (25.7±5.9 *vs* 26.5±4.9) and $\overline{PRP} \times 10^{-3}$ (16.7±3.3 *vs* 18.2±3.1) were not significantly different after training. From rest to maximum exercise level, as a group, patients were only able to double their maximum CSBF. Arterio-coronary sinus oxygen difference increased similarly before and after training (19% and 17% respectively). These increments were attributed to a displacement of the oxygen dissociation curve to the right. $\overline{PRP}$ was found to correlate better with CSBF before and after training (0.71 and 0.72 respectively) than indices which incorporate systolic ejection period per beat such as TTI and triple product. Heart rate was correlated differently with CSBF before training ($r = 0.64$) than after training ($r = 0.83$). The post-training increase of exercise tolerance in patients with angina pectoris is primarily due to a reduction of coronary blood flow requirement for a given workload. There is some indication that certain patients may also be able to increase symptom-limited exercise tolerance by increasing CSBF and $M\dot{V}O_2$.

ACKNOWLEDGMENTS

I would like to express my sincere thanks to Dr. R.B.J. Macnab, Faculty of Physical Education, University of Alberta, for his professional advice during this project and throughout my graduate program. I am also especially grateful to Dr. R.J. Ferguson, Director of the Exercise Physiology Laboratory at the Montreal Heart Institute who generously introduced me to the field of cardiovascular research and for his friendly advice, guidance and assistance throughout the experimentation and the drafting of my thesis. It was an honour to benefit from his vast experience and a great pleasure to work with Dr. Ferguson.

The realization of this study would not have been possible without the cooperation of a remarkable team. I would like to acknowledge: Dr. P. Côté and Dr. M.G. Bourassa, cardiologists, whose collaboration was essential throughout the study and especially during the hemodynamic evaluation; Miss Margot Méthé, registered nurse, who participated in the supervision of the training program and hemodynamic evaluations and whose professional and humanitarian approach gave security and confidence to the patients; Miss Elaine Tanguay and Mrs. Sandra Doyon-Fleury, who were involved in the supervision of the training program; Mrs. Lucille Ricard, Mr. André Grenier and Mr. Jean-Pierre Turcotte for their technical assistance; Mr. Benoît Roberge, engineer, who was responsible for the computer programming.

To all the subjects goes my expression of gratitude for making this study possible.

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CHAPTER I

INTRODUCTION

There is a lower functional exercise capacity (FEC) associated with an impairment in the clinical functional status of patients with coronary artery disease (CAD) compared to normal subjects of similar age, sex and habitual physical activity pattern (14). Bruce et al. (15) have found that the FEC was 24% lower than normal in men with healed myocardial infarction without angina pectoris. On the other hand, they report a much larger reduction (41%) in men with exertional angina, with or without evidence of prior infarction. However, the same basic physiologic problem was postulated in order to explain the lower FEC in both conditions; an imbalance between the myocardial oxygen supply and demand (109).

Although the basic problem is the same the factors leading to a reduction of FEC in both cases are different. In CAD patients without exertional angina, the limited stroke volume (SV) at the higher workloads has been found to be the major limiting factor of FEC (16). A reduced myocardial contractility in the hypoxic myocardium and the extent of infarcted myocardium could explain this decrease of SV. Furthermore, an other important factor might be a reduced maximal heart rate (HR). Bruce et al. (16) reported that reduced maximal HR was also a cardiovascular component associated with the lower FEC in this category of patients. However, with similar patients, Rousseau et al. (109) were unable to

observe a significant difference in maximal HR when their patients were compared to a control group. For CAD patients with angina pectoris, the main limiting factor is the low HR at which chest pain occurs (32).

Saphenous vein aortocoronary bypass surgery has succeeded in significantly increasing myocardial perfusion (57). Following surgery, angina pectoris is improved or relieved in 70 to 90% of patients (71, 129), exercise tolerance increased (2) and left ventricular function may be improved (11, 103). However, experience accumulated during the past five years indicates that the direct surgical approach has definite limitations (58, 85, 86, 87, 122). It is estimated that only 3 or 4 out of every 9 to 12 patients evaluated at coronary arteriography are candidates for aortocoronary bypass operations (122). Distal coronary artery obstructions with poor run-off and non contracting ventricular segments are the major factors limiting the scope of surgical treatment (86, 87, 122). Furthermore some patients refuse surgery. Of prime importance is the long-term function of the grafts (3). At one to two years after surgery, graft occlusion rates are reported to be approximately 20 to 25% (58, 85). Although surgical mortality is low, it is not negligible and intraoperative myocardial infarction is a problem of concern (58).

Physical training programs (TRN) have been repeatedly shown to improve the exercise capacity of selected CAD patients (18, 19, 25, 33, 34, 42, 46, 133, 135). With respect to the training of angina patients, Trap-Jensen and Clausen (133) found a two-fold increase in work time to angina threshold. Detry et al. (33) and Clausen and Trap-Jensen (19) demonstrated increases in symptom-limited maximal oxygen consumption ($\dot{V}O_{2_{sl}}$) of 21 and 32% respectively. The majority of these investigations

suggest that the benefits from TRN are the results of extracardiac adaptations (18, 19, 33, 135). Although the evidence is not conclusive, the available data strongly indicate that these functional improvements in angina patients with TRN are mainly due to reductions in myocardial oxygen consumptions ($M\dot{V}O_2$). These reductions are secondary to peripheral changes in skeletal muscles which tend to diminish the sympathetic circulatory stimulus with resultant decreases in HR and arterial blood pressure (BP) (18, 19, 33, 34). In addition, concomitant decreases in arterial BP and/or skeletal muscle vascular resistance would also tend to decrease $M\dot{V}O_2$ by lowering the afterload (101, 133). Several studies at symptom-limited maximum workload indicate that increase exercise threshold for angina patients after TRN could also be partly due to an enhanced coronary blood flow (CBF) or $M\dot{V}O_2$ (33, 34, 40, 99, 101, 117, 131, 133).

There is evidence that exercise conditioning in rats increases their coronary vascularity (131), maximum CBF and $M\dot{V}O_2$ (40, 117). Futhermore, Scheuer et al. (117) comparing the effects of increasing left atrial pressure on hearts of sedentary and conditioned animals in the working rat heart apparatus, demonstrated a greater increment of $M\dot{V}O_2$ in the trained group, and the difference observed was only achieved by the increase in CBF with no change in the extraction of oxygen across the myocardium. In human studies, evidence for an enhanced CBF following physical conditioning may be implied from reported increases of 10% (133) and 23% (101) in the maximum exercise pressure-rate product (PRP), increases of 7% for maximum exercise HR (33) and significant increases of maximal exercise triple product (TP) at the onset of angina (40).

RATIONALE BEHIND THE STUDY

Physical exercise is one of major stimuli to which the cardiovascular system is exposed. Pertinent hemodynamic data have been collected permitting a better understanding of the adaptations which take place during effort. Transition from rest to exercise is accompanied by increments in HR, cardiac output ($\dot{Q}c$), SV, systemic arteriovenous oxygen difference ($a\text{-}\bar{v}O_2$), oxygen consumption and by an important redistribution of blood toward active muscles (6). Faced with this higher and pressing demand of nutritive elements by skeletal muscles, the heart itself must be able to adapt in order to furnish its output and its own blood flow.

It has been found that the increase in $M\dot{V}O_2$ is not mainly determined by the external work of the heart but rather by the interplay of three major factors: the intra-myocardial tension, defined as the work performed by the contractile elements in stretching the elastic components, the contractile state of the myocardium which determines the velocity of the contraction, and the HR by which the effect is obvious since it determines the frequency at which the myocardial wall contracts (13, 127, 128). There is a close relationship between the parameters of left ventricular function during exercise and the major determinants of $M\dot{V}O_2$. Therefore, the heart must necessarily adapt for an increased ventricular activity during exercise by raising its own oxygen consumption. The dependence on oxygen supply for this energy requirement is one of the major characteristics of that muscle since it can only develop a small oxygen debt (13). The obligatory aerobic nature of myocardial metabolism means that cardiac energy utilization is directly related to

$M\dot{V}O_2$ (4, 5, 32).

However, direct assessment of $M\dot{V}O_2$ in man has been difficult. Basically it requires a precise invasive technique in order to measure artery coronary sinus oxygen difference (art-csO_2) and coronary sinus blood flow (CSBF). In an effort to circumvent this problem, investigators have employed indirect indices of $M\dot{V}O_2$ derived from animal studies. These indices are based on the factors which influence the intramyocardial tension and are easily measured; the developed pressure, the HR and the ejection time (32). Among the most frequently used indices are: the tension time index (TTI), which is the product of the HR and the area under the systolic portion of the ventricular, aortic or brachial pressure curve (116), the PRP which is calculated from ventricular, aortic or brachial artery systolic peak pressure times HR (105), and the TP which adds the systolic ejection period per beat (SEP/beat) to the PRP (101). However, it should be noted that none of these indices of $M\dot{V}O_2$ incorporates all the factors known to exert a significant influence on $M\dot{V}O_2$ (54). These indices ignore alterations in ventricular volume and inotropic state, both major determinants of $M\dot{V}O_2$ (101). Since these indices of $M\dot{V}O_2$ of CSBF are reproducible in predicting angina threshold for a given individual, it is reasonable to postulate that the omitted factors are either constant and/or vary in the same direction as HR and arterial BP (4, 102). It is usually accepted that the contractile state closely follows variations in HR and that ventricular volume would not change appreciably throughout exercise except in severe dysfunction of the left ventricle. Furthermore the relationship for the TP has been found to be consistant and independant of variations in the type, intensity and duration of exercise (105).

The best index to predict $M\dot{V}O_2$ during exercise seems to be the PRP. Recent studies show that the TTI and TP are less closely correlated with $M\dot{V}O_2$ than the PRP (68, 72, 82). The previously reported poor correlation of TTI with $M\dot{V}O_2$ during mild, supine exercise in humans has also been found by Kitamura et al. (82) during upright bicycle exercise. In well-conditioned, young normal subjects, data were obtained at two or three levels of exercise. There was a lower correlation ($r = 0.77$) between TTI and $M\dot{V}O_2$ than for PRP ($r = 0.90$) and $M\dot{V}O_2$. The maintenance of tension may be a relatively minor determinant of $M\dot{V}O_2$ (13). In addition, Holmberg et al. (68) have found a fourfold increase in $M\dot{V}O_2$ from rest to heavy supine exercise with a parallel fourfold increase in the PRP. This same linear relationship has also been observed by Kitamura et al. (82) during upright bicycle exercise. In addition, in their ten patients without angiographically demonstrable CAD, the coefficient of correlation between $M\dot{V}O_2$ and PRP was 0.88. Values for TTI were not reported.

This close relationship between $M\dot{V}O_2$ and PRP is also observed when the PRP is altered by nitroglycerin or beta blockade. Redwood et al. (102) have found that in such conditions angina occurs at a higher intensity of exercise but PRP at angina is unaltered. Following aortocoronary bypass surgery, no consistent change in TP has been found during exercise at a given workload (101). However, the maximal TP is markedly increased after surgery if the grafts are patent (4). The heart is an aerobic organ. The increase in the $M\dot{V}O_2$ with exercise is met by a higher myocardial blood flow and oxygen extraction from the coronary arterial blood (90). A comparison of the relative contribution of the two factors indicates that an increase in CBF is the major mech-

anism. The myocardium can only slightly increase oxygen utilization due to the relatively high arterial and art-csO_2 difference existing even at rest (37). Myocardial oxygen extraction during rest is approximately 70 to 75%, exceeding that of all other organs (90). In summary, CBF follows $M\dot{V}O_2$ pari passu as demonstrated in animal (37) and human (68, 82, 88, 104, 124) studies.

These results are in accordance with the hypothesis that indirect indices must be increased or decreased after an intervention that is known to increase or decrease CBF respectively. No data are presently available on CSBF determined at sitting rest and at different intensities of upright exercise up to the threshold of angina in CAD patients. Neither has the rest and exercise CSBF been determined before and after TRN.

PURPOSE OF THE STUDY

This study was designed to determine if CSBF and/or $M\dot{V}O_2$ is modified by four to six months TRN in patients with angina pectoris and angiographically documented CAD. The experimental conditions for the determination of CSBF before and after TRN were:

a) sitting rest

b) an equivalent individual submaximal workload

c) an equivalent individual submaximal HR

d) symptom-limited exercise.

LIST OF SYMBOLS

$a\text{-}\bar{v}O_2$: arterio-venous oxygen difference (ml/100 ml)

$art\text{-}csO_2$: arterial and coronary sinus oxygen difference (ml/100 ml)

BPd : brachial artery diastolic pressure (mmHg)

BPm : brachial artery mean pressure (mmHg)

BPs : brachial artery systolic pressure (mmHg)

CAD : coronary artery disease

CaO_2 : concentration of O_2 estimated directly in brachial artery (ml/100 ml)

$CaCO_2$: concentration of CO_2 estimated directly in brachial artery (ml/100 ml)

$CcsO_2$: concentration of O_2 estimated directly in the coronary sinus (ml/100 ml)

$CcsCO_2$: concentration of CO_2 estimated directly in the coronary sinus (ml/100 ml)

CBF : coronary blood flow

CSBF : coronary sinus blood flow (ml/min)

$\overline{CSP}$: mean coronary sinus pressure (mmHg)

CVR : coronary vascular resistance (mmHg/ml/min)

FEC : functional exercise capacity

FEV_I : forced expiratory volume for one second (liter)

HR : heart rate (beats/min)

Hb : hemoglobin (g/100 ml)

Ht : hematocrit (%)

LA : lactates (mg/100 ml)

$M\dot{V}O_2$: myocardial oxygen consumption (ml/min)

PaO_2 : partial pressure for O_2 measured directly in brachial artery (mmHg)

$PaCO_2$: partial pressure for CO_2 measured directly in brachial artery (mmHg)

$PcsO_2$: partial pressure for O_2 measured directly in the coronary sinus (mmHg)

$PcsCO_2$: partial pressure for CO_2 measured directly in the coronary sinus (mmHg)

PRP : pressure-rate product (units)

$\dot{Q}c$: cardiac output (liter/min)

SaO_2 : saturation of O_2 estimated directly in brachial artery (%)

$ScsO_2$: saturation of O_2 estimated directly in the coronary sinus (%)

SEP : systolic ejection period (sec)

SV : stroke volume (ml)

TRN : physical training program

TP : triple product (units)

TTI : tension time index (mmHg-sec/min)

VC : vital capacity (liter)

$\dot{V}O_2$ max : maximal oxygen consumption (liter/min or ml/kg X min)

$\dot{V}O_{2sl}$: symptom-limited maximal oxygen consumption (liter/min or ml/kg X min).

CHAPTER II

REVIEW OF LITERATURE

This review will focus on one aspect of the rehabilitation of CAD patients, namely the TRN of patients with a previous myocardial infarction and/or exertional angina pectoris. TRN has been used for approximatively 10 years in the rehabilitation of CAD patients and the effects of such therapy will be compared to results of TRN in controlled animal studies and in healthy sedentary subjects. Comparison with athletes will be avoided since differences between athletes and nonathletes, are not entirely due to TRN but also to the genetic endowment of the athlete which is particular to the requisites of each sport. Furthermore, the distinction between constitutional dissimilarities and the effects of TRN are not amenable to definitive analysis (1). For these reasons, only longitudinal studies are reviewed in this chapter. However, one must keep in mind that the longitudinal approach does not resolve all problems; volunteers are often athletic and differ from randomly selected normal people and patients. The exercise program can affect other variables such as body weight and smoking habits, and the results can be biased by dropouts (44).

PHYSICAL TRAINING OF HEALTHY SEDENTARY SUBJECTS AND ANIMALS

A) *Cardiorespiratory effects*

i) Maximal oxygen uptake

The primary measure of the quality of the cardiorespiratory system is maximal oxygen consumption ($\dot{V}O_2$ max) which depends on maximal $\dot{Q}c$ and the a-$\bar{v}O_2$ difference of the body. $\dot{V}O_2$ max reflects both the performance of the heart as a pump, the capacity of blood flow distribution and skeletal muscle oxygen utilization (91). The maintenance of arterial oxygen tension during heavy exercise demonstrates that pulmonary factors, ventilatory or diffusion, do not limit oxygen transport in normal subjects (92). For young untrained men, the mean value is approximatively 50 ml/kg X min, which diminishes with age to about 30 ml/kg X min at age 70 (106). In addition to age, interindividual variations in $\dot{V}O_2$ max are caused by sex (7), body size (92), habitual level of physical activity and a so-called ceiling effect or genetic potential (1, 75).

As a general finding, longitudinal studies on sedentary young males and females (79, 111, 112) and sedentary middle-aged males and females (60, 76, 79, 93, 94, 113, 123) have revealed that endurance-oriented TRN for several months increases $\dot{V}O_2$ max. In young males, studied in Dallas, (93) $\dot{V}O_2$ max increased from a value of 3.30 liter/min or 43 ml/kg X min before TRN to 3.91 liter/min or 51 ml/kg X min after TRN representing an increase of 19%. Saltin (111), in subjects of a similar age group ($\bar{X}$ = 21.6 years) found a 15.6% change in $\dot{V}O_2$ max after TRN. An improvement of only 10.9% for $\dot{V}O_2$ max was obtained in a group of twelve young healthy females ($\bar{X}$ = 23.7 years). In middle aged men, most studies (60, 63, 76, 94, 113, 123), have found an increase of $\dot{V}O_2$ max between 15% to 20% independant of the duration of their TRN. In the two longitudinal studies of longer duration, Hanson et al. (60) found an 18% improvement and Kasch et al. (76) a 17% increment over a training period of 7-months

and 2-years respectively. An increase higher than 30% for $\dot{V}O_2$ max has been reported by Pollock et al. (100) after a 20-weeks training period. However, this result can be partly explained by the lower pre-training $\dot{V}O_2$ as compared to other studies. In two groups of middle-age women, an increase of 13.2% of $\dot{V}O_2$ max has been observed in the youngest ($\overline{X}$ = 44.0 years) compared to 9.3% for the other ($\overline{X}$ = 56.4 years) after TRN (79).

Siegel et al. (123) postulated, in TRN of middle-aged men, that the number of sessions per week, the total duration of TRN, the effective duration of each session and the intensity of exercise influence the degree of improvement. Although the relative contribution of these components is still unclear, it can explain the lower relative improvement in increase for $\dot{V}O_2$ max in females of different age after TRN. Roskamm (107) mentions that sex does not appear to influence the result of TRN and, as stated above, the smaller improvement noted in women by Kiblom (79) is probably due to the less intensive TRN. It is of interest to note, that most TRN designed for men included periods at the maximal exercise level compared to the overall submaximal intensity used by Kiblom in women.

However, despite their relatively lower initial values, middle-aged men appear to be less trainable than younger subjects. Although the same relative increase in $\dot{V}O_2$ max was found in different age groups, as stated previously, improvement by older subjects tends to be less when their low $\dot{V}O_2$ max at the onset of training is taken into account. Saltin et al. (113) explain this less marked improvement in absolute terms by the ageing process rather than differences in amount of training done

by each age groups. Therefore, they emphasize that even if a middle-aged person has been sedentary during most of his life, he has the same relative ability as younger subjects to improve his $\dot{V}O_2$ max (113).

The increase in pulmonary ventilation is proportional to that in $\dot{V}O_2$ max, and since arterial blood gas studies indicate that ventilation and diffusion do not limit maximal performance under normal conditions, the increase in $\dot{V}O_2$ max with TRN is due to changes in its hemodynamic determinants and skeletal muscle cellular adaptation (32). The results of the few studies including hemodynamic data at the maximal exercise level show that the increased $\dot{V}O_2$ max after TRN in the young subjects (107, 111, 112, 137) is related to both an increase in $\dot{Q}c$ and in a-$\bar{v}O_2$ difference. In the older subjects (61) it was related only to an increased $\dot{Q}c$ since the a-$\bar{v}O_2$ difference was unchanged. Since in each case, the maximal HR was not increased but slightly reduced, the increased $\dot{Q}c$ results from an increase in SV. The reason why the maximal a-$\bar{v}O_2$ difference is not modified with TRN in middle-aged men is unknown(32). Data obtained in young and older women show that the increase in $\dot{V}O_2$ max results from a greater maximal $\dot{Q}c$ (80). However, because of the less intense TRN followed by women, the lack of increase in maximal a-$\bar{v}O_2$ difference with TRN in the young women might be simply due to the lower intensity of the TRN or/and less cellular adaptation.

A potential factor which could lead to an increased SV is an increase in heart volume. Astrand et al. (7) have found that a fairly good relationship exists in young adults between heart volume in supine position and the highest observed SV during exercise. However, one can find studies where increased maximal SV after TRN was associated with a

larger heart volume (112, 114), while in other studies the heart volume did not change or even significantly decreased after TRN (79, 108, 123). A larger heart volume after TRN has only been observed in young healthy subjects. In any case, it is clear that the SV can increase after TRN without any change in the resting heart volume. At this time, it is not possible to completely describe the mechanism responsible for the increase in SV (32). Therefore, in middle-aged men the SV increase is larger than can be expected from the heart volume enlargement, suggesting possible improvement in myocardial contractility (1). Although no definite explanation can be given for the reduced resistance in trained muscles during maximal exercise, Clausen (20) postulated that the increase in $\dot{Q}c$ maximum following TRN results from a decrease in total peripheral resistance. This implies that the increase in SV is a secondary event, due to the fact that $\dot{Q}c$ is greater at any HR after TRN.

The data collected in young sedentary subjects clearly indicate, however, that TRN can also increase the maximal $a\text{-}\bar{v}O_2$ difference. Since a greater redistribution of the maximal $\dot{Q}c$ can account for only a small fraction of this widened maximal $a\text{-}\bar{v}O_2$ difference, increased oxygen extraction capacity of the working muscles must be postulated (32). This higher oxygen extraction after TRN might by directly related to enzymatic changes in the skeletal working muscles (64). In fact, Holloszy (65) has shown that the mitochondrial fraction taken from the gastronemius muscle of trained rat displayed a two fold increase in the ability to oxidize pyruvate. Furthermore, increased oxygen extraction capacity of skeletal muscle after TRN might also be improved by an increase in the number and size of mitochondria (55).

ii) Response to submaximal exercise

At a given submaximal exercise level, $\dot{V}O_2$ is either unchanged or slightly lower after TRN while the ventilation is usually decreased (32). In the presence of the same $\dot{V}O_2$ for similar submaximal workloads post-TRN, total body mechanical efficiency remains unchanged (44). However, dramatic changes have been observed in hemodynamic determinants of $\dot{V}O_2$ so that a greater amount of external work can be performed at the same relative submaximal $\dot{V}O_2$ after TRN. TRN constantly reduces the HR at rest and at submaximal exercise levels (39, 47, 61, 113, 114). On the other hand, the effects of TRN on $\dot{Q}c$ are unclear. Where submaximal $\dot{V}O_2$ is constant, the lower HR was balanced by a higher submaximal SV and the $\dot{Q}c$ remained constant (47, 61, 112, 114). However, others have reported a slightly reduced $\dot{Q}c$ during submaximal work which was compensated by a widened a-$\bar{v}O_2$ difference (36, 39, 60). Saltin (112) pointed out that the lower submaximal $\dot{Q}c$ is not the most common finding in healthy subjects, and Detry (32) has made the observation that this result was not generally seen in sedentary subject but rather in well trained subjects studies before and after training season. Also, the effects of TRN on systemic arterial BP are not clear. Only small changes in the arterial BP are observed with TRN in young subjects (39, 61, 114). The common finding is that the brachial artery pressure is related to the HR at rest and during exercise, both before and after TRN (93). Adam et al. (1) pointed out that a slight reduction in arterial BP in middle-aged men with significant reduction in HR and little change in $\dot{Q}c$ in trainees at the same submaximal workloads. Reduced pressure must indicate that the contractile work of the left ventricle declines slightly.

In addition it must be postulated from submaximal results that peripheral adaptations to acute exercise secondary to TRN are important. Two major findings support this view. First of all, lactic acid (LA) concentration has been found to be constantly decreased in healthy young individuals, middle-aged men and coronary patients after TRN during submaximal exercise in spite of an unchanged or decreased $\dot{Q}c$ (44). Secondly, the distribution of the $\dot{Q}c$ at a given submaximal exercise level is probably modified. Recent studies have shown that at identical submaximal work intensities, the increase in working muscle perfusion is less pronounced and the flow to other tissues is less reduced in conditioned normal people and in CAD trainees (21, 130, 136). The lower level of blood LA in submaximal work may be due to an increased activation of red muscle fibers with a more efficient energy yield from aerobic processes (113). Lower muscle blood flow at the same submaximal workloads after TRN has also been explained by the considerably enhanced oxydative metabolic capacity in a trained muscle (47). Recent evidence showing increased activity of the skeletal muscle oxydative enzymes and an increase in the size and number of the muscle mitochondria after TRN (55, 64, 65) suggest that such a mechanism is operative.

This peripheral response to TRN is also important for two others reasons. For one, exercise testing using large trained muscle groups is an important prerequisite in order to observe significant training bradycardia. In two groups of young healthy subjects who performed arm training and leg training, respectively, Clausen et al. (22) found that arm training caused a pronounced reduction in HR during arm exercise, whereas only a small reduction was seen during exercise performed with non-trained leg muscles. Therefore, at the two submaximal

workloads which were chosen to give the same HR before TRN (*i.e.* 130 and 170 beats/min) during both leg and arm exercises, leg training reduced HR almost equally during leg exercise and arm exercises. In a previous study (23) it was reported that TRN performed with the legs did not reduce the group mean HR during arm work. However in two of eight subjects TRN of the leg muscles caused HR reduction during leg as well as arm work. This contradiction may be explained by fewer subjects and a less strenuous TRN (22). Clausen et al. (22) conclude from their results, that in addition to central circulatory changes there are alterations in the trained muscles that contribute to the training bradycardia. The other important point deals with $\dot{Q}c$ and its distribution which was unchanged in leg exercise with arm training and vice-versa (22).

B) *Cardiac function and metabolism*

Exercise training causes improved mechanical and metabolic performance of the rat heart. It has been demonstrated that hearts from conditioned rats have increased glycogen levels which can be mobilized but no changes were found in high-energy phosphate stores (118). Furthermore, the effect of increasing flow on left ventricular work, mean integrated left ventricular systolic pressure, $\dot{V}O_2$, LA production, and efficiency have been studied on hearts of sedentary and conditioned animals in the working rat apparatus (99). The hearts from conditioned rats showed a greater response in left ventricular work and mean integrated left ventricular systolic pressure as filling pressure was increased. It was also found that the maximal rate of left ventricular pressure rise was higher at each level of filling pressure. In the light of these findings these authors suggest an increase in the contractile state of the left ventricle of the trained rats, which may be due to an alteration

in the contractile proteins in the trained ventricles since cardiac actomyosin ATPase activities was increased (10).

The hearts from the trained rats also demonstrate a higher $M\dot{V}O_2$ and a lower LA production than hearts from the sedentary rats with similar increments of atrial pressure. In addition, it was found that the increase in $M\dot{V}O_2$ in the trained rats was due to an increase in CBF with no significant change in art-csO_2 difference; whereas, in the sedentary rats it was due to an increase in art-csO_2 difference with no significant change in CBF (117).

The response to hypoxia of hearts from sedentary and trained rats has also been studied (119). The hearts from trained rats maintained a higher left ventricular work and mean integrated left ventricular systolic pressure during hypoxia. However, during hypoxia, $M\dot{V}O_2$ and LA production were similar. Cardiac efficiency was twice as high during hypoxia in hearts of trained rats than in sedentary rats. Thus hearts of trained rats appear to be relatively more resistant to hypoxia, due to a more efficient mechanism of energy utilization. Similar data are not presently available on humans.

C) *Catecholamines*

Training may also affect catecholamine levels in the heart and in the adrenal glands, and the output of catecholamines in response to physical exercise. It has been shown in rats that TRN causes a significant decrease in total heart catecholamine content (31). Another study in rats showed that the norepinephrine content in the heart was lower in trained versus untrained rats, while the epinephrine content

in the adrenals is higher in trained rats (98). In man, the decreased HR at a submaximal workload has been shown to be due to a decreased cardiac sympathetic activity. With this respect the plasma level of norepinephrine, as an index of adrenergic activity during exercise, has been shown to increase during exercise in proportion to the relative workload (59). One of the principal sources of this norepinephrine appears to be in the accelerans fibers to the heart (134). Since after TRN, a given submaximal workload becomes a smaller relative workload, the level of cardiac sympathetic activity is decreased. In two recent studies, the effects of short term exercise training on plasma catecholamine levels done in normal subjects (134) and CAD patients (139) have focussed on two interesting points. The reduction of norepinephrine after TRN was best correlated with the concomitant reduction in HR. As the decrement in norepinephrine levels after TRN was significantly more pronounced during work performed with the trained muscle group, the conclusion was that local factors within the trained muscles as well as central factors (in the central nervous system and/or in the myocardium) were responsible for the significant decrement in arterial norepinephrine levels seen during exercise after TRN (134). In addition, Wolfson et al. (139) made the observation that decreased sympathetic activity in trained CAD patients seems unrelated to exercise tolerance.

PHYSICAL TRAINING IN THE THERAPY OF CORONARY ARTERY DISEASE

A) *Cardiorespiratory effects*

Increases in the FEC or $\dot{V}O_2$ max of asymptomatic patients (24, 27, 33, 34, 101) or the $\dot{V}O_{2sl}$ of patients with angina pectoris (19, 33, 46, 101, 109, 110) is well documented. However improvement in $\dot{V}O_{2sl}$

seen in angina patients appears to be more impressive than the increment observed in $\dot{V}O_2$ max for patients without angina after TRN. In a study by Detry et al (33) $\dot{V}O_{2_{sl}}$ was obtained in six patients with angina and six with prior myocardial infarction but without angina. In the patients with angina $\dot{V}O_{2_{sl}}$ increased 30% from 19 ml/kg X min before TRN to 24 ml/kg X min after TRN. In the patients without angina $\dot{V}O_2$ max increased 18% from 27 ml/kg X min to 32 ml/kg X min. As in healthy subjects, the most important increases were in patients who had the lowest pre training $\dot{V}O_2$ max or $\dot{V}O_{2_{sl}}$

According to Detry (32), increased $\dot{V}O_{2_{sl}}$ of angina patients after TRN results from the decreased HR, arterial BP and thus myocardial oxygen requirements during exercise; the workload precipitating the anginal pain before TRN is indeed performed after TRN with lower $M\dot{V}O_2$ and the anginal pain does not appear at this level of exercise. The hemodynamic mechanisms underlying the increase of $\dot{V}O_2$ max in patients without angina of effort is less clear. A cross-selectional study done by Rousseau et al. (109) report that the higher $\dot{V}O_2$ max of trained patients with healed myocardial infarction resulted almost exclusively from a greater maximal a-$\bar{v}O_2$ difference. There is presently no satisfactory explanation for this result in such patients (109).

B) *Response to submaximal exercise*

i) Heart rate, cardiac output and arteriovenous oxygen difference

It has been shown in several investigations (19, 24, 33, 46, 110) that the HR at a given submaximal workload, as seen in healthy subjects, is consistantly reduced after TRN in CAD patients. Frequently accompanying this lower HR is a reduced systemic arterial BP (19, 24, 33).

As HR and arterial BP are important determinants of $M\dot{V}O_2$, it is postulated that a CAD patient will perform a given submaximal exercise with a presumably lower $M\dot{V}O_2$.

More controversial results are presently available concerning other hemodynamic responses accompanying the lower HR after TRN in these CAD patients. According to some authors, the lower post-training HR is compensated by an increase in the SV with an unchanged $\dot{Q}c$ and $a\text{-}\bar{v}O_2$ difference during submaximal exercise loads after TRN (24, 46, 48, 110); others found a decreased $\dot{Q}c$ attended by an increased $a\text{-}\bar{v}O_2$ difference during same submaximal workloads after TRN (33, 109, 125). The relative importance of central and peripheral circulatory changes for the improved performance after exercise training is still debated. Frick et al. (48) state that the finding of unchanged $a\text{-}\bar{v}O_2$ difference during exercise after TRN reflects enhanced SV due to improve contractility and muscular hypertrophy. On the other hand, Clausen and Trap-Jensen (19) state that the reduction in $\dot{Q}c$ for a given submaximal $\dot{V}O_2$ after TRN to be due to improvement of the peripheral oxygen extraction; the decreased $\dot{Q}c$ being secondary to the improved peripheral utilization of oxygen.

The resolution of these controversial results is not yet satisfactory, but a large part of the contradictions could be explained by factors related to the experimental procedures and/or selection of patients. At first examination of experimental procedures, major differences can be detected in the supine position used by Frick et al. (46, 48) versus the upright position mentioned in other studies; and in the time interval between the acute myocardial infarction and the onset of TRN, which was much smaller in the studies by Frick et al. (46, 48). Gauthier

(52) found no difference in hemodynamic responses between supine exercise and upright bicycle exercise at the same submaximal workloads before and after TRN in CAD patients. The changes observed in $\dot{Q}c$, SV and $a\text{-}\bar{v}O_2$ difference were of the same order and direction. However, it seems that the time interval between the myocardial infarction and the onset of training is important since the increase in submaximal SV with training in early post-myocardial infarct period is largely nonspecific and corresponds mostly to the natural evolution of the cardiac function during the first months after myocardial infarction (110).

In addition to the delay between the myocardial infarction and the onset of training, it seems that both age and the question of whether or not angina pectoris is present are of importance for the effect of training. Bjernulf (12) found an increase in SV only in the younger age group (<55 years) of trained patients. This SV increase during submaximal exercise after TRN was still more pronounced in the younger patients without angina of effort. Therefore, he pointed out the possibility that these observations might only reflect the lower training intensity in the older patients and those with angina pectoris. However, it seems possible that TRN produces the central type of effect in some patients with CAD and the peripheral type in others, and this could be a function of the severity of the disease (12).

ii) Distribution of cardiac output

The distribution of the submaximal $\dot{Q}c$ after TRN is pratically the same as was observed in healthy subjects. It has been demonstrated that at a given level of submaximal exercise, the estimated splanchnic blood flow was higher and the submaximal muscle blood flow lower after

TRN in CAD patients (19). Considering that the mechanical efficiency has not changed after TRN, higher oxygen extraction capacity of the working muscle must have contributed to the same submaximal $\dot{V}O_2$ after TRN. The mechanism underlying this adaptation is probably based on an increased enzymatic activity of the muscles as observed in healthy subjects (32).

C) *St-segment depression*

The magnitude of St-segment depression is generally regarded as reflecting the degree of myocardial ischemia. In this respect, it is not surprising that investigators have been interested in studying the relationship of St-segment depression to either a given level of submaximal exercise (34, 109) or the same submaximal HR (27, 78), PRP (34) or TP (101) at the onset of angina, before and after TRN. It is a well recognized fact that the magnitude of the St-segment depression at the same submaximal workloads is decreased after TRN (34, 109). This is probably attended by a lesser metabolic demand on the heart. However, at the same HR values before and after TRN conflicting results have been observed. Costill et al. (27) found that the St-segment depression occured at the same HR both before and after TRN, but Kavanagh et al. (78) and Kasch and Boyer (77) have observed in some CAD patients after TRN of longer duration, less St-segment depression at a specified exercise HR.

At the onset of angina, Detry and Bruce (34) found that TRN altered the relationship between angina and St-segment depression as manifestations of myocardial hypoxia during exercise. Exertional angina occurred at a higher PRP after TRN but developed St-segment depression at the same PRP as before TRN. On the other hand, Redwood et al. (101)

found higher TP values at the onset of angina, and in none of the three patients in whom St-segment changes developed during exercise did the degree of St-segment depression at the onset of angina after TRN exceed that observed at the onset of angina before TRN.

D) *Coronary collaterals*

An hypothesis that collateral circulation could be enhanced by exercise in man with partially obstructed coronary arteries was suggested by Eckstein (38) who showed that TRN induced coronary collateral circulation in dogs with prior partial ligation of the circumflex arteries. However, Kaplinsky et al. (74) could not demonstrate a similar training effect in dogs where the anterior descending was completely obstructed. They observed collateral vessels development in both trained and controlled dogs. In man, the presence of collaterals has been shown to correlate with the severity of coronary obstructive disease and that collaterals have not been demonstrated cinearteriographically in patients without CAD or in those with less than 50% reduction in lumen (84). The development or addition of new collaterals after training in man does not receive support from recent studies (26, 43). Ferguson et al. (43) studied 14 patients with significant obstructions (50% or greater) in one, two or three coronary arteries who exercised three times a week for 13 months. The appearance of new collateral vessels after TRN in only two patients was related to existing lesions progressing to complete occlusion. This is in agreement with Conner et al. (26) who indicated, from repeat arteriographic evaluations, that collateral vessels developed only with an increase in severity of the local disease. However, one can question the validity of the angiographic technique which can visualize

the coronary network only in the resting condition where the threshold stimulation for opening collaterals is perhaps too low. In addition, it cannot be ruled out that CBF through existing collaterals may be increased since flow is not measured by the coronary angiographic technique.

E) *Coronary blood flow and myocardial oxygen consumption*

i) Measurement of myocardial blood flow

Although appreciable progress has been realized during past years, the measure of coronary blood flow in human still remains very difficult. In general, methods can be subdivided in two groups: those requiring coronary sinus or coronary artery catheterization and others where cardiac catheterization is not necessary. In the first category the major difference when coronary sinus instead of coronary artery catheterization is done is the use of venous sampling techniques compared to precordial counting techniques. Another distinction between these techniques is the nature of tracer used. Tracers most often employed are nitrous oxide, kripton, xenon, hydrogen, helium and argon. In addition regarding precordial counting techniques a radioactive tracer must be used. In the second group of methods, the principle lays in the notion of myocardial clearance elaborated by Sapirstein (115). The indicator is an isotopic tracer quantitated following intravenous administration by external count at a precordial level.

In spite of their respective advantages, all these methods present multiple disadvantages. They do not permit serial determinations and the detection of rapid variations of coronary flow. Since the indicator used is not entirely atoxic there may be a limitation as to number of determinations possible (83). Most of these methods have not been

validated against an independant standard such as right heart bypass and in addition this validation when myocardial flow is abnormally heterogeneous as for instance in CAD patients is almost inexistant. Except for the venous sampling techniques $M\dot{V}O_2$ cannot be derived.

Beside these techniques, the principle of thermodilution with catheterization of the coronary sinus has been successfully employed to determine CSBF. This method derives from that described by Fegler (41). Basically, it requires continuous injection of a thermal indicator at constant speed. Numerous advantages are associated to this technique. According to Ganz (50), this method permits measurements to be repeated in short intervals since the body acts as a large sink and rapid changes in coronary circulation can be studied. The blood flow of the coronary sinus so measured is expressed in ml/min instead per 100 grams of myocardium. Although right heart catheterization might be a disadvantage, the possibility of sampling coronary venous blood is important if one is interested in data regarding myocardial metabolism. Finally, the equipment is inexpensive and simple. The only limitation of importance is related to the precise position of the catheter within the coronary sinus. As carefully pointed out by Klocke (83) misleading changes in flow can occur if catheter position within the coronary sinus changes, either in response to an intervention or as a result of catheter softening. Ganz (51) has presented data validating the accuracy of the thermodilution method in model experiments and in vivo studies in the canine jugular vein and coronary sinus. A good reproducibility of measurement in man (4.0±2.4%) has been found with 20 patients when CSBF were performed within three minutes at rest.

ii) Response to exercise training

There is only indirect evidence that the maximal CBF and/or $M\dot{V}O_2$ during upright exercise is increased following TRN in man. This piece of evidence refers to the maximum PRP (124, 133) and TP (40, 101) during upright exercise that has been shown to increase in patients with angina pectoris following TRN. Sim and Neill (124) have reported no change with TRN for the myocardial LA production at the angina threshold during step-wise atrial pacing. In addition, the $M\dot{V}O_2$ and CBF were unchanged at a paced HR ten beats below the angina threshold (124). Therefore, a significant higher PRP evaluated during upright exercise position at the onset of angina after TRN was interpreted to indicate that TRN exerted a specific effect and did not carry over to a different stress such as pacing-induced tachycardia (124).

In order to explain this higher maximum PRP after TRN observed during exercise, these authors suggest that a change in the myocardial contractile state, operative only in exercise but not atrial pacing, would have changed the relationship between $M\dot{V}O_2$ and PRP (124). This is yet to be proved since PRP determined with an intra-arterial catheter during submaximal upright bicycle exercise has been found to correlate highly with $M\dot{V}O_2$ under normal conditions (82) and following changes in contractility secondary to Propranolol (72). Clausen (20) has proposed two explanations why angina is provoked at a higher product of HR and arterial BP after TRN. First of all a decrease of one or more of the other determinants of $M\dot{V}O_2$ allows higher values for PRP to be achieved at the same $M\dot{V}O_2$. Secondly, there is a higher maximum $M\dot{V}O_2$ due to improve O_2 supply to the region of the myocardium from which ischemic

pain is provoked. According to Detry (34) these findings of higher PRP, TTI or TP at the onset of angina after TRN are difficult to interpret, since the electrocardiographic data after TRN do not suggest an improved oxygen supply to the myocardium. Hellerstein (62) has pointed out that psychological changes induced by TRN could also play a role by modifying the threshold of pain perception.

In respect to elucidate the significance of the higher PRP at the onset of angina after TRN, it is important to study the relationship between submaximal and maximal PRP and CSBF and/or $M\dot{V}O_2$ while the patient is exercising, since the adaptation seems to be restricted to exercise (124).

CHAPTER III

METHODOLOGY

PATIENTS SELECTION

Fourteen male patients not accepted for or refusing coronary artery surgery were selected for this study according to the following criteria: a) history of disabling but stable angina pectoris, b) angina pectoris during upright exercise, c) significant obstruction (≥70%) of one or more major vessel at selective coronary arteriography, d) adequate left ventricular function at rest with left ventricular end-diastolic pressure ≤15 mmHg and ejection fraction ≥0.50, e) willingness to participate in the TRN and test procedures, and f) no other disability incompatible with exercise training. One patient, after the pre-TRN test procedures, decided to withdraw from the study at the beginning of TRN for personal reasons. The clinical and angiographic characteristics of the fourteen patients selected are presented in Table 1. The mean age was 46 years (range: 33-58). Four patients had slight ventricular dyskinesis at ventricular angiography and five had a prior myocardial infarction. All had abnormal St-segment depression on a multistage treadmill test which was terminated by chest pain. Two patients were receiving antihypertensive treatment. All patients were in sinus rhythm, and no patient had signs or symptoms of left ventricular failure. Two patients had triple, seven double, and five single coronary vessel obstruction (≥70%).

TABLE 1. Patient description

Patient	Age (yr)	Ht (cm)	Wt (kg)	Fc	Prior MI	Angina (mo)	BP (mmHg)	Ventricular function	Coronary disease ≥50% AD	LC	RC
GB	40	170	64.2	III		120	152/72	normal		65	100
LB	52	164	76.4	I	+	9	190/130	normal	85	75	100
HD	50	164	66.0	II	+	5	142/90	normal	95		85
RF	50	177	79.0	II		5	110/70	normal			95
PG	39	175	66.5	II	+	7	142/100	normal	70	60	100
YL	33	166	75.7	III		36	120/80	normal		75	90
JL	57	174	63.5	II		2	142/80	hypokinesis			100
GL	58	178	82.4	II		6	134/90	normal	100		100
LG	35	172	56.5	II		2	132/76	hypokinesis	100	90	50
LR	40	162	58.0	I	+	4	124/70	hypokinesis	95		80
CS	44	168	66.0	II		39	128/76	normal	90	70	75
RS	56	161	66.0	II		36	152/100	hypokinesis			100
MV	46	171	69.0	II	+	6	142/80	normal	90	50	100
CB	48	168	81.0	II		24	162/120	normal		65	85

Abbreviations: MI = myocardial infarction; BP = resting blood pressure; AD = anterior descending coronary artery; LC = left circumflex coronary artery; RC = right coronary artery

All were being treated on an out-patient basis and as volunteers were asked to participate in the study. Informed consent (Appendix A) was obtained after the purpose of the study, testing manipulations to be performed and associated risk were fully explained. Patients were also free to drop out of the study at any point. Lastly, all patients had sedentary habits, with the absence of intense physical activity during the last ten years.

EXPERIMENTAL DESIGN

Hemodynamic data were collected during four specific conditions before and after TRN: during sitting rest, at an equivalent submaximal workload, at an equivalent submaximal HR and at symptom-limited exercise (exertional angina or exhaustion). Before TRN the two submaximal levels were arbitrarily chosen according to the HR obtained from a previous multi-stage bicycle ergometer test. The first and second level of submaximal exercise were individually adjusted to produce a HR of approximately 15 and 5 beats respectively below the predetermined symptom-limited exercise HR. After TRN the submaximal levels were performed such that the first workload was identical to the second level pre-TRN. The second workload post TRN was chosen to produce the same HR as the second level pre-TRN.

PROCEDURES

A) *Multi-stage bicycle ergometer test*

The main purpose of this non-invasive test was to determine the HR and PRP provoking angina (symptom-limited exercise capacity) or

exhaustion. This test was repeated in the middle and at the end of TRN. It also served to individually prescribe the TRN intensity on the bicycle ergometer.

The test was conducted on a bicycle ergometer (Monark). The workload was initially adjusted at 225 kgm/min for two minutes after which it was, without interruption, increased by 75 kgm/min every two minutes until termination according to predetermined limiting symptoms. For each patient this test was always done twice with a 15 min rest interval. Only the second test was used in the data analysis, the previous one being specifically used for familiarization (Appendix B).

The HR was continuously monitored by means of a digital tachometer (Exercise cardio-tachometer, Quinton Inst, model 609) and with an oscilloscope (Physio-sentinel, Mennen-Greatbatch Inc., model 808-005). The EKG was recorded on an electrocardiograph (Sanborn 500, Viso-Cardiette) using a bipolar lead (CM_5) and the arterial BP was determined by auscultation during the last 15 sec of each minute and at the onset of chest pain or immediately preceding the cessation of exercise.

B) *Hemodynamic evaluation*

i) Familiarization study

The day before the catheterization study, pre and post TRN, each patient performed two bouts of bicycle ergometer exercise for approximately 12 min at the work intensities previously mentioned. This familiarization served to determine if the patient could sustain the sub-angina workloads for up to 12 min.

ii) Catheterization study

The patient was hospitalized the night preceding the hemodynamic evaluation. Patients were studied without premedication in the morning at least two hours after a light meal. The thermodilution and arterial catheters were inserted with the patient in the supine position. The patient was then seated on the bicycle ergometer and the position of the thermodilution catheter in the coronary sinus was verified by an X-ray image amplifier. Resting measurements were taken followed by the first submaximal exercise period. A rest interval of 15 min preceded the second submaximal exercise. After the completion of the measurements at this workload the intensity was gradually increased to the threshold of angina at which time a final series of determinations were taken.

Procedures during sitting rest

1. calibration for thermodilution thermistors and arterial BP recordings
2. thermodilution curve recordings with simultaneous recording of mean arterial BP (BPm)
3. calibration for arterial and coronary sinus pressures
4. BPm, systolic arterial (BPs), diastolic arterial (BPd) pressure and mean coronary sinus pressure ($\overline{CSP}$) recordings (25 and 100 mm/sec)
5. Simultaneous sampling of coronary sinus and arterial blood for analyses of pH, PO_2, PCO_2, LA, hemoglobin (Hb) and hematocrit (Ht).

Procedure during exercise

The same procedure was followed during exercise beginning at the fifth minute. In addition duplicate measurements were done in some patients during the first workload before TRN and during the second workload after TRN in order to calculate the reproducibility of CSBF determinations. In those cases, the second series of measures was a repetition of steps one through four, and was performed immediately following blood sampling (i.e. step 5).

LABORATORY TECHNIQUES

A) *Coronary sinus blood flow by thermodilution*

i) Introduction of catheters

With the patient in the supine position a superficial vein located in the antecubital area of the right or left arm was dissected after local anesthesia by infiltration of chlorhydrate of Lidocaine (2%). A no. 8F Ganz thermodilution catheter (0.75 mm internal diameter) was then inserted into the coronary sinus and immediately connected to the venous transducer. The tip of the catheter was positioned in the coronary sinus using an image intensifier (Picker X-ray, Pectronic "800"). The position of the catheter was again verified with the patient seated on the ergometer prior to the resting measurements. The external thermistor was placed just inside the coronary sinus in order to include flow from the posterior interventricular vein and to avoid contamination with right atrial blood. The verification involved the injection of a contrast material to outline the coronary sinus. Systematically the catheter position was checked prior to and during exercise.

A no. 18 Amplatz catheter (Becton-Dickinson), was introduced percutaneously in the right or left brachial artery using a metallic guidewire. The catheter was immediately connected to the arterial transducer. A multilead (112) EKG tracing was recorded at regular intervals and monitored continuously on an oscilloscope (Sanborn, model 769).

The catheters were firmly fixed to the arm of the patient and covered with sterile dressing. In order to prevent blood coagulation in the catheters the pressurized system, composed of a pressure bag (fenwal), was filled with heparinized (0.05 ml/100 ml) isotonic saline.

ii) Injection system recording

The leadwire cable for both internal and external thermistors of the thermodilution catheter was connected to a preamplifier (CA-105, Wilton-Webster Labs) which was joined to the Wheatstone Bridge (CB-204, Wilton Webster Labs). The output of dual channel Wheatstone Bridge was recorded by two DC coupling amplifiers (Sanborn, 4500 series recorder) at a paper speed of 10 mm/sec. The thermodilution catheter was connected to two 20 ml syringes mounted on a double action pump (Harvard withdrawal-infusion pump model 907) filled with pre-cooled isotonic saline solution at 20 to 22^{o}C. A few ml of solution were introduced into the catheter and a period of one minute was allowed for equilibration of the bridge. After the base lines were established for both thermistors a constant injection at 38 ml/min was begun. The injection was stopped after a definite plateau was reached for both curves (~ 20 seconds) which were simultaneously visualized on the oscilloscope and

recorded on photographic paper (Kodak, type 1801).

iii) Thermodilution catheter calibration

The thermistors were pre-calibrated by establishing experimentally a curve with resistance (ohms) against temperature (^{o}C). An example of a typical curve is presented in Appendix C. The tip of the catheter was submerged in an isotonic serum solution which was continuously stirred in order to maintain a constant temperature. The temperature of the solution was varied by adding melted ice or warm serum and was measured with a mercury thermometer (sensitivity $1/5^{o}C$). The measurements were done each $0.5^{o}C$, from $20^{o}C$ to $40^{o}C$ for the internal thermistor and from $30^{o}C$ to $40^{o}C$ for the external thermistor. They were repeated twice for each thermistor, one in increasing stages and one in decreasing stages.

iv) Calculations

The CSBF was determined by the Ganz thermodilution technique (51). The principle of the method is based on the assumption that the heat lost from the system between the site of injection and the site of detection is negligible and, therefore, that the heat lost by the blood equals the heat gained by the injectate. The corresponding mathematical equation is:

$$(Fb)\ (Sb)\ (Cb)\ (Tb - Tm) = (Fi)\ (Si)\ (Ci)\ (Tm - Ti)$$

(heat lost by blood) (heat gained by injectate)

where

Fb and Fi = volumes (ml) of blood and indicator respectively participating in heat exchange during a definite period

Tb, Ti and Tm = temperature of blood, injectate, and mixture of blood and injectate (^{o}C)

Sb and Si = specific density of blood and injectate respectively (g/cm^3)

Cb and Ci = specific heat of blood and injectate respectively ($cal/g/^{o}C$)

For a period of 60 sec the formula is expressed as following:

$$Fb = Fi \underset{(A)}{\left(\frac{Si \times Ci}{Sb \times Cb}\right)} \underset{(B)}{\left(\frac{Tm - Ti}{Tb - Tm}\right)} \quad ml/min$$

The product (A) is considered constant such as:

$$\left(\frac{Si \times Ci}{Sb \times Cb}\right) = 1.08$$

It has been demonstrated that although Cb varies with the hematocrit, this approximation is adequate (45). The final formula for computation of CSBF was:

$$CSBF = 38 \times 1.08 \left(\frac{Tb - Ti}{Tb - Tm} - 1\right) \quad ml/min$$

v) *Reproducibility of measurements*

The reproducibility of CSBF determinations during the exercise conditions was evaluated by comparing paired determinations at submaximal exercise for a similar PRP ($\pm 1 \times 10^{-3}$ units). Calculations

showed a standard error of measurement (SEM)[1] of 13.6 ml for an error of 8.6% (Appendix D).

B) *Blood pressures*

Pressures from the brachial artery and coronary sinus were recorded on an optical recorder with two P23Db Statham transducers (Statham Instruments Inc.). Prior to recording, the base lines for both transducers were established immediately before the catheters were put in communication with their respective transducer. Arterial BPs, BPd, BPm and $\overline{CSP}$ obtained by electrical integration were recorded over at least two respiratory cycles at paper speeds of 25 and 100 mm/sec. Furthermore arterial BPm was recorded during CSBF measurement.

The zero reference point for pressure measurement in the sitting position was adjusted to the fourth intercostal space at the sternal edge (69). Before the first measurement, a static calibration of both transducers was obtained with a mercury manometer (Trimline, PyMatt, Corp.) such that a pressure change of 100 mmHg produced a deflection of 100 mm on the records.

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[1] According to Dahlberg (30)

$$SEM = \sqrt{\frac{\Sigma d^2}{2n}}$$

where

d = difference between first and second measures

n = number of paired measurements

$$\text{error in } \% = \frac{\frac{SEM \times 100}{\overline{X}_1 + \overline{X}_2}}{2}$$

where

$\overline{X}_1$ and $\overline{X}_2$ = means of first and second measurements.

C) *Blood parameters*

Analyses of arterial and coronary sinus blood pH, PO_2, PCO_2, Hb, Ht and LA were carried out within one hour on samples withdrawn anaerobically in heparinized syringes and stored immediately in ice.

i) pH, PO_2, PCO_2

Analyses for pH, PO_2 and PCO_2 were done on a digital blood gas analyzer (ABL1, Radiometer, Copenhagen). This apparatus determines pH by a micro-method with the utilization of a glass electrode and a Columel reference electrode (49). The PCO_2 and the PO_2 are determined by means of a Severinghaus electrode for CO_2 and a Clark electrode for O_2. A complete calibration was automatically and continuously repeated every two hours. This was done for pH by mean of two buffers at 6.841 and 7.383 and for PCO_2 with two references gas at 5.61% and 11.22% CO_2. Complete analysis of each sample required 0.5 cc of blood.

In order to test the reproducibility of measurements, twenty samples done in duplicata in our laboratory have shown the following SEM: pH = 0.004, PCO_2 = 0.45 mmHg, PO_2 = 3.12 mmHg for a percentage error of 0.1%, 1.2%, 2.2%, respectively (Appendix D).

ii) Blood lactates

Coronary sinus and arterial LA determinations were made at rest and during each level of exercise. A semi-automated technique was employed for determinations using a Technicon Auto Analyzer, which is a modification of the manual method described by Friedland and Dietrich (63). The blood samples at each condition were immediately prepared by using a 1.15 dilution of whole blood according to the method of Somogyi

(126). Then samples were immediately frozen at -20°C until analysis. Before each series of determinations for a patient, the Auto Analyzer was calibrated by mean of a standard solution of lactic acid (0.40 mg%) obtained from Sigma. This solution was diluted at various concentrations graded from 2 to 20 mg% in order to establish a standard reference curve. With samples values over 20 mg% further dilution was made and appropriated correction factor calculated. Duplicate determinations taken at rest and at one level of exercise before TRN have shown the following SEM: 0.067 at rest and 0.314 at exercise for a percentage error of 1.2% for both conditions (Appendix D).

iii) Hemoglobin and hematocrit

The Hb was determined by means of 0.04 ml of blood mixed with 80 ml of Isoton (1:500). After 1 ml of this solution was removed, six drops of an hemolytic agent (ZAP-OGLOBIN) was diluted with this specimen. The hemolytic agent converts the Hb to Cyanmethemoglobin and the resulting color, proportional to Hb content was read on a hemoglobinometer (Coulter Electronics Inc.) in gm%. The Ht was measured with a Coulter Counter (model ZBI) according to the Coulter principle which is based on the determination of the number and size of blood cells by electrical gating (17).

iv) Plasma catecholamines

Arterial plasma catecholamines were measured on seven patients at sitting rest and at an equivalent submaximal workload pre and post TRN. Concentrations were measured according to an adaptation of the method of Coyle and Henry (29) which is a modification of the radiometer enzymatic assay technique for tissue catecholamines. Blood sam-

ples for catecholamines were collected at the same time as the other blood samples and immediately centrifuged at -2°C, 14,000 rpm for 20 minutes. The plasma was transferred to another chilled tube. Plasma proteins were precipitated and the plasma-acid mixture was agitated on a Vortex for 30 sec, then centrifuged and stored in a refrigerator until assay.[2]

D) *Calculated values*

Coronary sinus and arterial blood oxygen content ($CcsO_2$ and CaO_2 respectively) were calculated from hemoglobin concentration and PO_2 using an oxyhemoglobin dissociation curve with correction for pH and temperature according to Severinghaus (120). The same normal oxygen dissociation curve was assumed after TRN since Shappell et al. (121) have shown that training does not change oxygen affinity of blood. $\dot{M}VO_2$ was calculated as the product of CSBF and art-csO_2 difference. Coronary vascular resistance (CVR) was calculated by dividing arterial BPm minus $\overline{CSP}$ by CSBF.

Furthermore four indices reflecting myocardial oxygen requirements or CSBF were computed: PRP was calculated from brachial artery systolic peak pressure time HR (105). Arterial BPc was measured as the average result of ten consecutive complexes at paper speeds of 25 mm/sec. Mean PRP ($\overline{PRP}$) was calculated from BPm times HR. TP was calculated from brachial artery BPs times HR times SEP/beat (101). SEP was taken

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[2] These secondary data were obtained through a collaborative study with Drs. Jacques De Champlain and Daniel Cousineau, Department of Physiology, University of Montreal.

from the onset of the pressure wave to the incisura and was measured as the average result from five consecutive complexes at paper speeds of 100 mm/sec. Lastly, TTI was calculated from brachial artery mean systolic pressure times HR times SEP/beat. Brachial artery mean systolic pressure was measured by the average result of five consecutive tracings of systolic portion of brachial artery pressure where areas were automatically integrated. These data were computed using a Hewlett-Packard computer (model 9830A) with a digitizer (model 9864A).

CONDITIONING PROGRAM

The patients lived at home and came to the gymnasium two to five days a week for exercise training. During the first two weeks, each patient was submitted to either two consecutive bouts of twelve minutes of leg exercise or one bout each of leg and arm exercises. There was a five minute rest interval between bouts. The leg exercise consisted of pedalling in the sitting position on a bicycle ergometer. Arm exercise (cranking) was the same type of movement as leg exercise with the patient seated and the center of the pedal revolution at the level of the heart. Bicycle exercise was preferred since it allows a better control of exercise intensity. Arm exercise was inserted in the TRN of six patients in order to investigate a special problem not directly related to this study. The starting workloads were individually adjusted in relation to the patients exercise capacity. This initial workload represented approximately 70% of the maximal workload (legs: $\bar{X}$=384 kgm/min; arms: $\bar{X}$=262 kgm/min (Appendix E)). After two weeks, the training sessions were extended with a period of adapted volleyball of equal duration (~ 25 minutes). The intensity of exercise was increased gradually dur-

ing the TRN in an attempt to maintain each patient at a subanginal level of work (Figure 1).

The interval between pre and post TRN studies ranged from 16 to 26 weeks. The attendance varied between two and three sessions per week with an average of 2.6 sessions per week. However one patient RF discontinued TRN for two weeks as all other regular activity due to a nervous breakdown. He returned to train for five weeks before post TRN evaluation. Two patients used sublingual nitroglycerin before each TRN session. When angina occurred during bicycle exercise, sublingual nitroglycerin was given. Although no need for emergency care was required, medical personnel and special equipment such as a defibrillator were ready for immediate use.

STATISTICAL ANALYSIS

Comparisons between the three periods of testing for the multi-stage bicycle ergometer data were done by a one-way analysis of variance for repeated measures along with a Newman-Keuls a posteriori test (138). Summary tables of these analyses are presented in Appendix F.

In order to do comparisons pre to post TRN at sitting rest, at an equivalent submaximal workload, at an equivalent submaximal HR and at maximum CSBF, data were tabulated such as presented in Appendix G. Students t-test for paired data were employed to analyze the difference between pre and post TRN for each experimental condition. The same inferential test was used to analyze differences in some variables between rest and maximum exercise. Two patients JL and RS were ex-

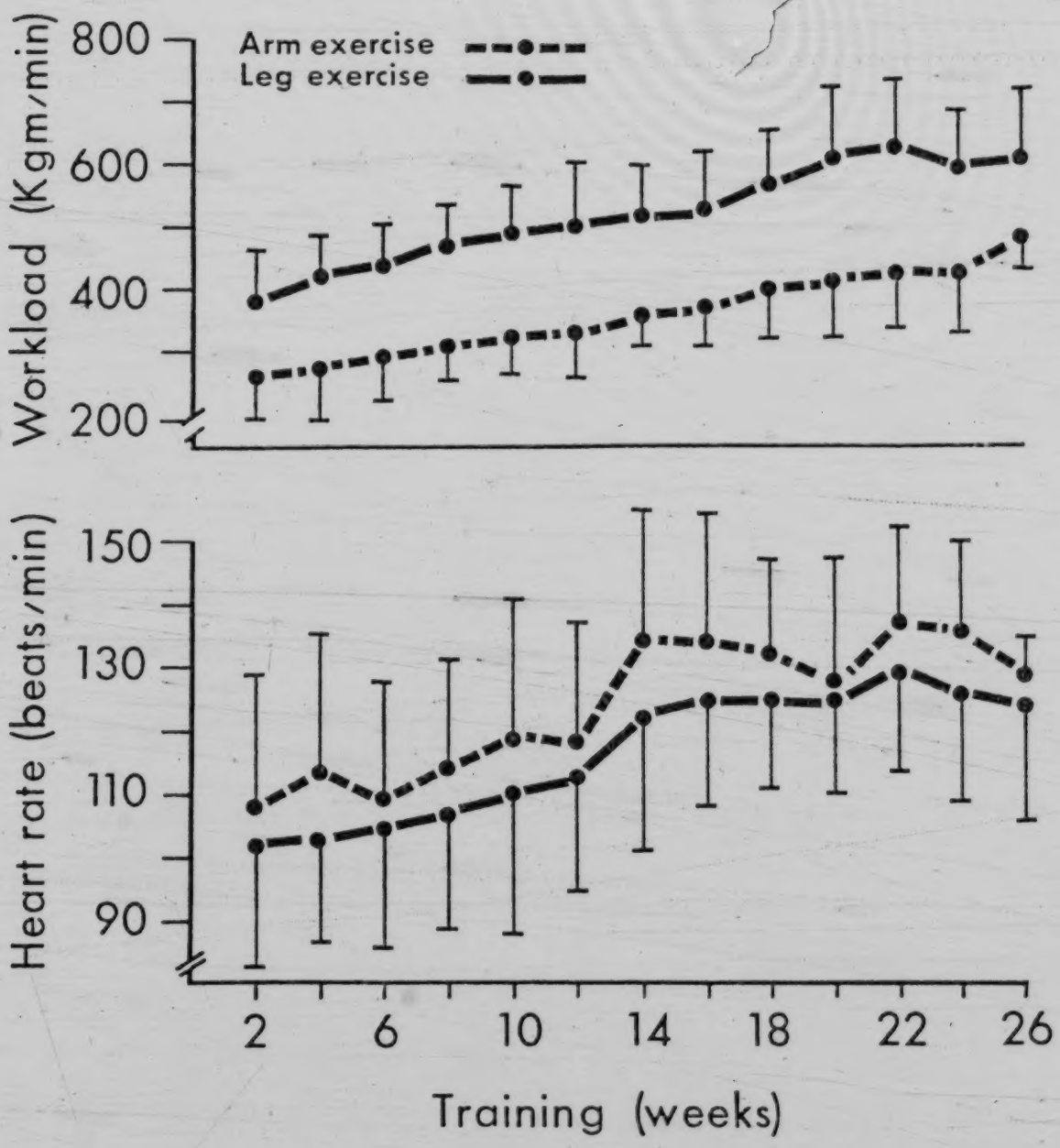


Fig. 1. Heart rate and workload evolution during training.

cluded from those comparisons for reasons discussed below.

Finally, all raw data obtained in the four conditions previously described, including occasional duplicate measurements, were stored on tape as shown in Appendix H. With CSBF and $M\dot{V}O_2$ as dependent variables Pearson Product Moment correlations were computed with $\overline{PRP}$, PRP, HR, arterial BPs, workload, CVR, TTI, and TP as dependent variables. All computations were done using a Hewlett Packard digitizer (model 9864A) in conjunction with the model 9830A computer at the Montreal Heart Institute.

CHAPTER IV

RESULTS

EFFECT OF PHYSICAL TRAINING PROGRAM

A) *Functional exercise capacity*

The maximal workload on a standardized multi-stage bicycle ergometer test has shown an increment of 23% at the mid-TRN period and a 39% increase for the overall period of TRN (Table 2). The major augmentation was found in the early phase of TRN with a significant increase of maximal workload ($p<0.01$) from a mean value of 559±113 kgm/min to 688±189 kgm/min at the mid-TRN period. A tendency for a higher maximal workload at the end of TRN was noted but the difference was not significant compared to the mid-TRN period. Changes were observed regarding the duration of the test with a 40% increase at the mid-TRN period with no further increment by the end of TRN. Concerning the hemodynamic variables measured or calculated, TRN significantly ($p<0.01$) increased the maximum PRP X 10^{-3} by 22% from a mean initial value of 24.6±4.5 to 30.0±5.9 by the end of TRN. This maximum PRP was almost entirely due to a parallel change in maximal HR in presence of a slight tendency of maximal arterial BP to increase. The maximal HR increased by 12% from an initial mean value of 130±15 beats/min compared to 145±15 beats/min at the end of TRN. Although a significant increase was observed for maximum PRP and HR these changes occurred mainly after the mid-TRN period whereas the major change in maximal workload took place in the first half of the TRN.

Table 2. Maximal Multi-Stage Bicycle Ergometer Test Data

n = 11	TRAINING		
	Pre	Mid	Post
Workload (kgm/min)	559±113	688±189	775±221
	p<0.01	NS	
Heart rate (beats/min)	130±15	133±14	145±15
	NS	p<0.01	
BP systolic* (mmHg)	193±17	196±24	206±31
	NS	p<0.01	
PRP X 10^{-3} (units)	24.6±4.5	26.2±4.6	30.0±5.9

* Systolic blood pressure determined by auscultation.

Regarding basic anthropometric and respiratory measurements done before and after TRN, no significant changes were observed for weight; vital capacity (VC) and force expiratory volume for 1 sec (FEV_1) (Table 3). TRN did not significantly alter the sum of four fat skinfolds.

B) *Training program*

The intensity of the workload prescribed during the TRN sessions was adjusted so that the patient was able to tolerate the exercise without chest pain. The mean values for TRN workload during leg exercise, recorded each two weeks, almost doubled by the end of TRN changing from 384±78 kgm/min to 600±109 kgm/min. In addition, it was possible to interrupt propranolol, in the six patients using it, by the end of the sixteenth week of TRN (Appendix D).

C) *Hemodynamic study*

Patients were evaluated before and after TRN using arterial and coronary sinus catheterization at sitting rest and at three different levels of standardized bicycle exercise: at an equivalent submaximal workload, at an equivalent submaximal HR and at symptom-limited exercise level. At sitting rest a significant decrease ($p<0.05$) of HR was found with a mean initial value of 78±9 beats/min dropping to 70±5 beats/min at the end of TRN[3] (Table 4). Except for resting HR, mean values of all

[3] Two patients RS and JL were excluded from the pre and post comparisons hemodynamic data due to technical problems experienced in the positioning of the coronary sinus catheter. In one patient the catheter was consistently expelled from the coronary sinus at rest and in another in whom fluoroscopy in the upright position was not used prior to TRN, CSBF values were presumed to be great cardiac vein before TRN and total left ventricular after TRN.

TABLE 3. Basic anthropometric and respiratory measures at rest pre (I) and post (II) training.†

	n	I	II	P*
Weight (kg)	12	68.0±8.0	68.0±7.0	NS
VC (liter)	9	4.1±0.5	4.1±0.5	NS
FEV_1 (liter)	9	3.4±0.5	3.4±0.5	NS
FEV_1/VC (%)	9	82.9±10.3	84.4±9.6	NS
Σ of 4 skinfolds (mm)	11	50.4±24.7	45.5±10.6	NS

† Values are mean ± standard deviation

* P is for Student's t-test for paired values

Abbreviations: VC = vital capacity; FEV_1 = forced expiratory volume for 1 sec

TABLE 4. Mean coronary hemodynamics data† at sitting rest pre (I) and post (II) training.

n = 10	I	II	P*
HR (beats/min)	78±9	70±5	$p<0.05$
BPs (mmHg)	149±19	139±17	NS
BPd (mmHg)	86±11	84±10	NS
BPm (mmHg)	112±16	107±16	NS
mean BPs (mmHg)	135±19	132±19	NS
$\overline{CSP}$ (mmHg)	3±3	3±3	NS
SEP/beat (sec)	0.25±0.02	0.26±0.02	NS
CSBF (ml/min)	95±25	90±17	NS
$M\dot{V}O_2$ (ml/min)	10.7±4.3	10.2±2.9	NS
art-csO_2 (ml/100 ml)	11.04±1.77	11.18±1.62	NS
CVR (mmHg/(ml/min))	1.17±0.29	1.18±0.19	NS
PRP X 10^{-3} (units)	11.8±2.1	10.1±1.5	NS
$\overline{PRP}$ X 10^{-3} (units)	8.4±1.8	7.5±1.6	NS
TP X 10^{-3} (units)	29.5±5.0	25.7±3.9	NS
TTI X 10^{-3} (units)	26.5±5.1	24.1±4.0	NS

† Values are mean ± standard deviation

* P is for Student's t-test for paired values

Abbreviations: HR = heart rate; BPs, BPd, BPm = brachial artery systolic, diastolic, and mean pressure; $\overline{CPS}$ = mean coronary sinus pressure; SEP = systolic ejection period; CSBF = coronary sinus blood flow; $M\dot{V}O_2$ = myocardial oxygen consumption; art-csO_2 = arterial coronary sinus oxygen content difference; CVR = coronary resistance; $\overline{PRP}$ = mean PRP.

other variables were not significantly different between pre and post TRN. Mean values for CSBF and $M\dot{V}O_2$ were 95±25 ml/min and 10.7±4.3 ml/min respectively before TRN compared to 90±17 ml/min and 10.2±2.9 ml/min after TRN.

At an equivalent submaximal workload ($\overline{X}$ ~ 400 kgm/min) CSBF was significantly ($p<0.05$) lower after TRN dropping from a mean value of 163±36 ml/min to 138±21 ml/min (Table 5). Although $M\dot{V}O_2$ diminished by 16%, the difference was not significant ($p<0.10$). Mean values for HR and arterial BPm, BPs and BPd were all significantly lower after TRN. Directly related to these results were significant decreases in PRP with TRN. Calculated from arterial BPs and BPm respectively values were 22.1±3.8 ($X\ 10^{-3}$) to 17.8±3.7 ($X\ 10^{-3}$) and 15.2±2.7 ($X\ 10^{-3}$) to 12.3±2.6 ($X\ 10^{-3}$). Although SEP/beat was significantly ($p<0.05$) increased, the net effect on TP and TTI was unimportant so that these indices were also significantly lower after TRN. Similarly, mean values for arterial LA concentration (Table 6) decreased significantly with TRN (26.7±10.5 mg% to 20.3±13.2 mg%).

At an equivalent submaximal HR ($\overline{X}$ ≈114 beats/min) the mean value for workload was increased from 344±92 kgm/min to 506±90 kgm/min (Table 7). Despite this 76% increase in workload for the same HR, all the coronary hemodynamic measures, systemic pressures and indices of $M\dot{V}O_2$ were essentially the same. The only other significant difference at this exercise condition was a higher mean value for arterial LA concentration after TRN compared to pre TRN value with 31.4±16 mg% and 24.0±13.9 mg% respectively (Table 6). As a result of the unchanged arterial BP and SEP/beat, all indirect-indices were of similar values for pre and post TRN.

Table 5. Mean coronary hemodynamic data at an equivalent submaximal workload (mean ~ 400 kgm/min) pre (I) and post (II) training

n = 9	I	II	P*
HR (beats/min)	120±14	103±11	p<0.01
BPs (mmHg)	180±25	168±30	p<0.05
BPd (mmHg)	89±15	83±16	p<0.05
BPm (mmHg)	126±20	119±21	p<0.05
mean BPs (mmHg)	155±30	144±30	p<0.01
$\overline{CSP}^{\div}$ (mmHg)	5±2	6±4	NS
SEP/beat (sec)	0.23±0.02	0.25±0.03	p<0.05
CSBF (ml/min)	163±36	138±21	p<0.05
$M\dot{V}O_2$ (ml/min)	20.1±5.2	17.3±3.6	NS
art-csO_2 (ml/100 ml)	12.31±2.12	12.70±1.63	NS
CVR (mmHg/(ml/min))	0.77±0.14	0.86±0.21	NS
PRP X 10^{-3} (units)	22.1±3.8	17.8±3.7	p<0.01
$\overline{PRP}$ X 10^{-3} (units)	15.2±2.7	12.3±2.6	p<0.01
TP X 10^{-3} (units)	49.9±10.7	45.9±11.3	p<0.01
TTI X 10^{-3} (units)	44.0±10.7	39.4±10.4	p<0.01

Symbols and legend similar to Table 4.

$\div$ (n = 8)

TABLE 6. Mean arterial blood lactate data[†] and catecholamines concentrations at sitting rest and various levels of exercise pre and post training (TRN).

	lactates (mg%)				catecholamines (ng/ml)			
	n	pre-TRN	post-TRN	P*	n	pre-TRN	post-TRN	P
I[‡]	9	5.9±1.7[‡]	5.6±1.3	NS	7	0.702±0.243	0.746±0.129	NS
II	10	26.7±10.5	20.3±13.2	<0.01	6	1.501±0.451	1.249±0.364	<0.01
III	8	24.0±13.9	31.4±16.8	<0.05	-	-	-	
IV	7	31.9±15.8	52.4±31.9	NS	-	-	-	

† Values are mean ± standard deviation

* P is for Student's t-test for paired values

‡ I = sitting rest; II = equivalent submaximal workload; III = equivalent submaximal heart rate; IV = maximum coronary sinus blood flow.

TABLE 7. Mean coronary hemodynamic data at an equivalent submaximal heart rate (mean ∿ 114 beats/min) pre (I) and post (II) training.

n = 8	I	II	p*
Workload (kgm/min)	344±92	506±90	p<0.01
BPs (mmHg)	173±28	176±31	NS
BPd (mmHg)	86±19	83±21	NS
BPm (mmHg)	124±22	122±23	NS
mean BPs (mmHg)	156±27	154±28	NS
SEP/beat (sec)	0.23±.03	0.24±0.03	NS
CSBF (ml/min)	156±32	145±24	NS
$M\dot{V}O_2$ (ml/min)	19.2±4.2	18.7±3.7	NS
art-csO_2 (ml/100 ml)	12.55±2.30	12.89±1.80	NS
CVR (mmHg/(ml/min))	0.78±0.14	0.82±0.22	NS
PRP X 10^{-3} (units)	19.9±2.6	20.3±3.9	NS
$\overline{PRP}$ X 10^{-3} (units)	14.1±2.3	13.9±2.6	NS
TP X 10^{-3} (units)	45.2±9.1	49.0±12.7	NS
TTI X 10^{-3} (units)	40.7±8.9	43.0±11.3	NS

Symbols and legend similar to Table 4.

Pre and post TRN comparisons at the maximum level of exercise done at the onset of angina or fatigue. Mean values for maximal HR, CSBF, $M\dot{V}O_2$, PRP, TP and TTI tended to be higher post TRN but the differences were not significant. The maximum workload was significantly augmented from an initial mean value of 505±101 kgm/min to a post TRN mean value of 705±170 kgm/min (Table 8). Although workload was greatly increased, maximum arterial LA concentration was not significantly higher ($p<0.10$) after TRN with a post TRN mean value of 54.8±25 mg% compared to 31.3±13.5 mg% at the pre TRN evaluation. However $\overline{CSP}$ was significantly higher after TRN.

Catecholamine levels were obtained in certain patients at sitting rest and at an equivalent submaximal workload (Table 6). At rest similar mean values were observed at pre and post TRN evaluation. However the catecholamine level after TRN (1.249±0.364 ng/ml) was significantly lower than pre TRN value (1.501±0.451 ng/ml) for a given submaximal workload.

EVOLUTION OF HEMODYNAMIC AND HEMATOLOGIC VARIABLES WITH EXERCISE

From rest to maximal exercise values HR increased by 67%, $M\dot{V}O_2$ by 132%, CSBF by 108%, art-csO_2 difference by 19% at pre-TRN evaluation (Figure 2). These increments were accompanied by a simultaneous decrement of CVR of 80%. After TRN, changes in the same direction and of similar magnitude were found for $M\dot{V}O_2$, CSBF and art-csO_2 difference with a percentage change of 148%, 127% and 17% respectively. Regarding HR a signigicantly ($p<0.05$) greater increment was found after TRN (103%).

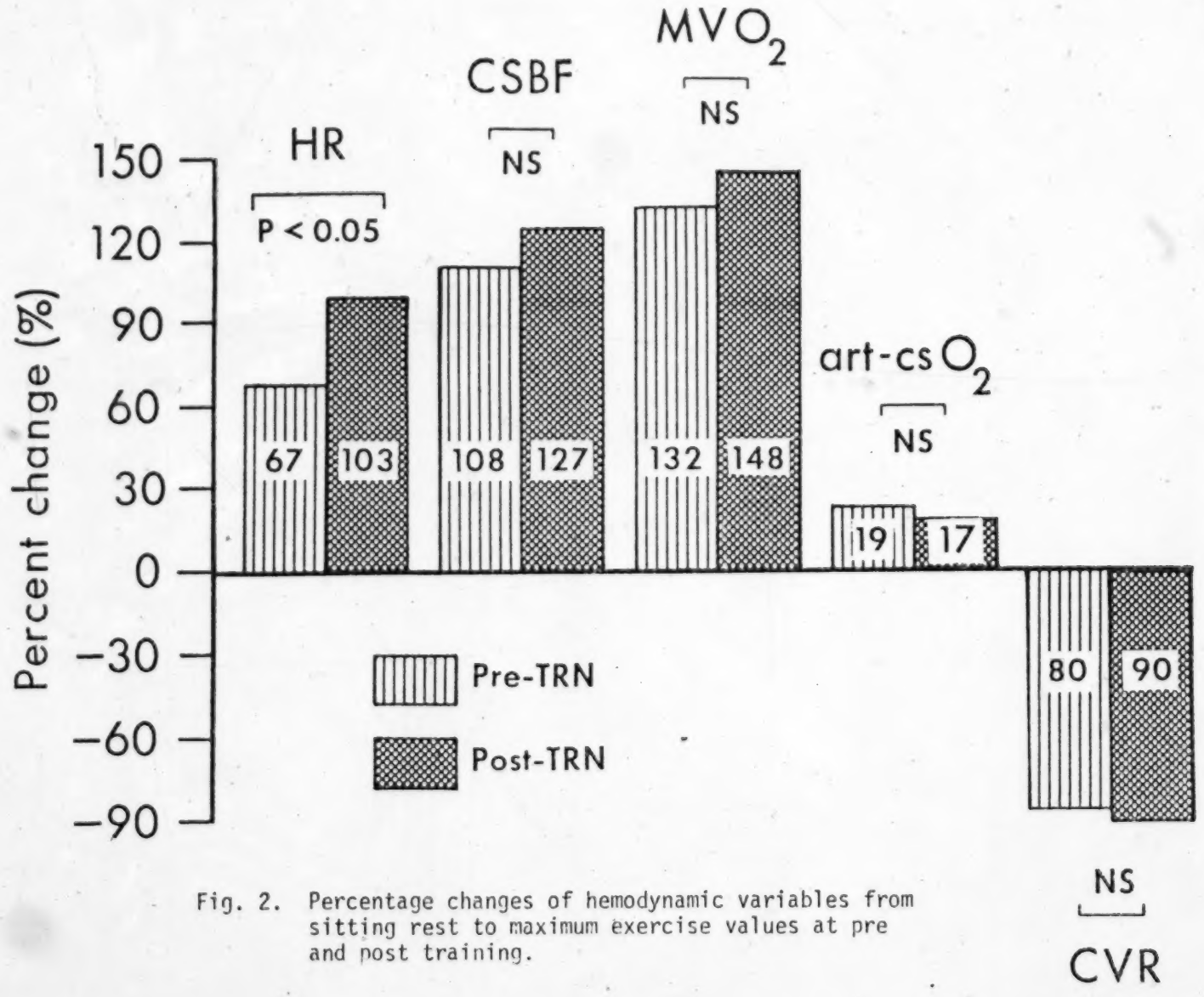


Fig. 2. Percentage changes of hemodynamic variables from sitting rest to maximum exercise values at pre and post training.

TABLE 8. Mean coronary hemodynamic data at maximal CSBF pre (I) and post (II) training.

n = 11		I	II	P*
workload (kgm/min)	11	507±101	705±170	p<0.01
HR (beats/min)	11	130±17	141±21	NS
BPs (mmHg) ∓	8	184±27	184±31	NS
BPd (mmHg) ∓	8	87±12	89±19	NS
BPm (mmHg)	11	128±21	130±16	NS
mean BPs (mmHg) ∓	8	153±24	163±23	NS
$\overline{CSP}$ (mmHg) ∓	7	7±2	9±4	p<0.05
SEP/beat (sec) ∓	8	0.21±0.02	0.22±0.03	NS
CSBF (ml/min)	11	195±52	205±49	NS
$M\dot{V}O_2$ (ml/min) ∓	8	25.7±5.9	26.5±4.9	NS
art-csO_2 (ml/100 ml) ∓	8	13.10±1.89	13.44±1.55	NS
CVR (mmHg/(ml/min))	11	0.67±0.14	0.63±0.18	NS
PRP X 10^{-3} (units) ∓	8	24.5±4.5	26.5±4.7	NS
$\overline{PRP}$ X 10^{-3} (units)	11	16.7±3.3	18.2±3.1	NS
TP X 10^{-3} (units) ∓	8	51.9±7.9	56.3±13.1	NS
TTI X 10^{-3} (units) ∓	8	44.9±6.2	49.3±9.8	NS

Symbols and legend similar to Table 4.

∓ (n = 8)

Pre-TRN arterial oxygen content (CaO_2), arterial oxygen saturation (SaO_2) and (PaO_2) were not significantly different at maximum CSBF compared to mean resting values (Tables 9 and 10). However after TRN, although PaO_2 and SaO_2 did not changed, CaO_2 was slightly higher ($p>0.05$). $PcsO_2$ was not different before TRN between rest to maximum CSBF values. The same result was observed after TRN. Interestingly coronary sinus oxygen content ($CcsO_2$) and coronary sinus oxygen saturation ($ScsO_2$) were significantly decreased. At pre-TRN evaluation, $CcsO_2$ dropped from mean resting value of 8.5±1.4 ml/100 ml to 6.8±1.4 ml/100 ml at maximum CSBF and $ScsO_2$ from 41.7±7.1% to 33.2±7.7%. Similar significant decreases were observed for $CcsO_2$ and $ScsO_2$ after TRN. Arterial and coronary sinus pH were found to be significantly lower at maximum CSBF compared to rest at pre and post TRN with the exception of arterial pH before TRN where the difference was found to be not significant. Hb was similar at rest and at maximum CSBF before as well as after TRN.

MEASURES OF RELATIONSHIP

The Pearson product-moment correlation coefficient for CSBF and $\dot{M}VO_2$ with hemodynamic variables and indices were calculated before and after TRN. Regression equations and coefficients were computed for all data and for exercise data only (Table 11, 12, 13). High correlation coefficients were observed between CSBF and $\dot{M}VO_2$ pre and post TRN considering all data ($r = 0.88$ and $r = 0.95$ respectively) and without rest data ($r = 0.82$ and $r = 0.90$ respectively).

Regarding correlations with CSBF, the highest coefficients were found before TRN for PRP, $\overline{PRP}$ and CVR with $r = 0.78$, $r = 0.7\bar{T}$ and

TABLE 9. Mean blood data† changes from sitting rest to maximum CSBF before training.

n = 8	rest	maximum CSBF	p*
CaO_2 (ml/100 ml) ∓	19.6±1.0	20.0±1.0	NS
$CcsO_2$ (ml/100 ml)	8.5±1.4	6.8±1.4	p<0.01
SaO_2 (%)	97.1±1.4	96.3±1.4	NS
$ScsO_2$ (%)	41.7±7.1	33.2±7.7	p<0.01
PaO_2 (mmHg)	100±11	98±12	NS
$PcsO_2$ (mmHg)	24±2	22±3	NS
Hba (gms)	14.9±0.8	15.2±0.7	NS
Hbcs (gms)	14.9±0.9	15.2±0.7	NS
$PaCO_2$ (mmHg)	30±4	32±2	NS
$PcsCO_2$ (mmHg)	39±7	47±4	p<0.05
pHa (units)	7.44±0.05	7.38±0.04	NS
pHcs (units)	7.40±0.04	7.32±0.03	p<0.02

† Values are mean ± standard deviation

* P is for the Student's t-test for paired values

∓ (n = 7)

Abbreviations: CaO_2, $CcsO_2$ = concentration of oxygen in brachial artery and coronary sinus; SaO_2, $ScsO_2$ = saturation in oxygen in brachial artery and coronary sinus; PaO_2, $PcsO_2$, $PaCO_2$, $PcsCO_2$ = partial pressure for oxygen and carbone oxyde in brachial artery and coronary sinus; Hba, Hbcs = hemoglobin in brachial artery and coronary sinus.

TABLE 10. Mean blood data† changes from sitting rest to maximum CSBF after training.

n = 9	rest	maximum CSBF	P*
CaO_2 (ml/100 ml)	18.8±1.0	19.2±0.8	p<0.05
$CcsO_2$ (ml/100 ml)	7.6±1.2	5.8±1.2	p<0.05
SaO_2 (%)	96.4±0.8	96.1±1.0	NS
$ScsO_2$ (%)	38.9±6.4	29.3±6.0	p<0.02
PaO_2 (mmHg)	92±8	93±8	NS
$PcsO_2$ (mmHg)	25±6	21±3	NS
Hba (gms)	14.6±0.7	14.8±0.7	NS
Hbcs (gms)	14.4±0.8	14.7±0.6	NS
$PaCO_2$ (mmHg)	34±3	30±2	p<0.01
$PcsCO_2$ (mmHg)	44±4	48±2	NS
pHa (unit)	7.43±0.03	7.37±0.04	p<0.02
pHcs (unit)	7.40±0.03	7.30±0.04	p<0.01

Symbols and legend similar to Table 9.

Table 11. Correlations (r) and regression coefficients of CSBF with several variables pre (I) and post (II) training (all data).

Variables	I				II			
	r†	n	slope	intercept	r	n	slope	intercept
$\dot{M}VO_2$	.88	65	6.253	36.202	.95	51	6.967	19.253
$\overline{PRP}$	.71	73	9.404	27.125	.72	49	7.530	45.382
PRP	.78	67	7.258	14.075	.72	49	5.041	50.909
HR	.64	73	1.468	-8.620	.83	49	1.402	-7.279
TTI	.61	67	3.105	35.990	.53	48	2.096	64.519
TP	.67	67	2.775	31.142	.59	48	1.987	59.206
CVR*	.72	72	-.847	5.742	.88	49	-1.089	5.873
Workload	.27	61	.099	129.801	.64	40	.158	78.501
BPs	.60	67	1.063	-26.053	.35	49	.529	58.941

* log 10 of CSBF
† all correlation values significantly different from zero ($p<0.05$)

Abbreviations: $\dot{M}VO_2$ = myocardial oxygen consumption; $\overline{PRP}$ = mean PRP; CVR = coronary vascular resistance; BPs = brachial arterial systolic blood pressure.

Table 12. Correlations (r) and regression coefficients of CSBF with several variables pre (I) and post (II) training (without rest data).

Variables	I				II			
	r†	n	slope	intercept	r	n	slope	intercept
$\dot{M}VO_2$	.82	53	6.015	42.171	.90	36	6.700	23.132
$\overline{PRP}$	.62	61	8.899	35.671	.50	40	5.350	79.064
PRP	.73	55	7.501	8.358	.54	40	4.255	69.752
HR	.52	61	1.465	-7.754	.74	40	1.406	-7.789
TTI	.49	55	2.541	62.825	.24≠	39	1.031	116.384
TP	.59	55	2.710	39.605	.31	39	1.193	102.471
CVR*	.77	61	-1.255	6.027	.78	40	-0.925	5.760
BPs	.53	55	.883	12.847	.08≠	40	.113	141.682

Symbols and legend similar to Table 11.

≠ (NS ($p>0.05$))

Table 13. Correlations (r) and regression coefficients of $\dot{MVO}_2$ with several variables pre (I) and post (II) training (all data).

Variables	I				II			
	r†	n	slope	intercept	r	n	slope	intercept
$\overline{PRP}$	.69	65	1.222	2.330	.76	45	1.144	3.210
PRP	.71	62	.865	1.8693	.73	45	.716	4.882
HR	.52	65	.160	1.255	.84	45	.306	-3.983
TTI	.63	62	.395	3.436	.54	44	.292	6.923
TP	.65	60	.336	3.614	.58	44	.270	6.4506
CVR*	.48	73	-1.341	4.157	.60	49	-1.394	4.1689
Workload	.12≠	53	.0064	18.560	.72	36	.027	6.832
BPs	.58	54	.1320	-4.456	.09≠	37	.011	16.276

Symbols and legend similar to Table 11.

≠ (NS ($p>0.05$))

r = 0.72 respectively (Table 11). A similar pattern was observed when rest data were excluded although respective coefficients were somewhat lower (Table 12). After TRN, higher correlation coefficients were also found with the three previously mentioned parameters using both, all data and without rest data conditions. However a considerable difference was observed for the correlation coefficients with HR before and after TRN. After TRN, in both these conditions coefficients were r = 0.83 and r = 0.74 respectively. On the other hand, the corresponding coefficients before TRN were r = 0.64 and r = 0.52. Furthermore it was observed that the indices which include the SEP/beat were poorer correlates of CSBF. As a general rule, correlation coefficients between $M\dot{V}O_2$ with the same parameters and indices as those used with CSBF gave results in similar direction but of lower magnitude (Table 13).

CHAPTER V

DISCUSSION

The thermodilution method is particularly suited to the measurement of CSBF during exercise. A single determination can be obtained in one or two minutes permitting the evaluation of CSBF prior to and at the onset of angina pectoris with a minimum of risk and discomfort to the patient. The rapidity of measurement and the determination of absolute left ventricular coronary blood flow overcome the major disadvantages of the inert gas techniques where relatively long periods of saturation or desaturation are necessary and where regional differences in flow per unit weight, such as in patients with coronary artery stenosis, tend to give overestimates of CBF (83).

However, of major concern in the utilization of the thermodilution method is the position of the catheter in the coronary sinus, since this will determine the portion of left ventricular coronary flow which is measured (83, 51). For exercise studies in the supine position Bahler and Macleod (8) advanced the catheter and measured great cardiac vein blood flow in patients with severe obstructions of the left anterior descending artery. Bertrand et al. (9) reported that the thermodilution catheter position was extremely stable during relatively intense supine exercise in normal subjects when the external thermistor was placed at the proximal portion of the coronary sinus as described by Ganz (51). The latter position was adopted for the present study. According to Ganz (51), in normal hearts about two-thirds of the total coronary sinus flow drain through the great cardiac vein and one third comes from the

posterior wall. Furthermore, the coronary sinus drains almost exclusively the left ventricular and the intraventricular septal myocardium. In fact, it has been found that only 17% of the small veins draining into the coronary sinus arise outside the left ventricular system (70).

The reproducibility of repeat determination of CSBF on the same day during supine rest is approximately 5% (28, 51). No significant difference was found in resting CSBF values obtained when coronary sinus catheterization was repeated within a one week period (125). In the present study duplicate determinations of CSBF were performed on various patients during the same exercise period when the $\overline{PRP}$ was constant (i.e. within $\pm 1 \times 10^{-3}$ units). The reproducibility of duplicate determinations was 13.6 ml/min or 8.6% of the mean. There was no difference between the mean of the first and second determinations (158 and 157 ml/min). When the data for the first two exercise levels of Jorgensen et al. (73) were calculated using the same formula the CSBF reproducibility of the nitrous oxide method was comparable (11%).

Throughout the experimental procedure we found that the catheter could change position in some patients. It was often necessary to verify the catheter position by fluoroscopy prior to each exercise workload. It is possible that the catheter position could have varied during exercise in some patients before and after TRN, however, the lack of significant difference in CSBF during sitting rest and during exercise at the same HR and $\overline{PRP}$ with TRN suggest that this was not the case to any great extent.

Since the thermodilution method measures absolute coronary flow from the left ventricle and not flow per unit weight of heart

muscle, it is difficult to compare values with those obtained by inert gas techniques. Our mean CSBF values at rest in the upright position (90 to 95 ml/min) are lower than those reported for the supine position by Ganz et al. (51) (128 ml/min) and Soliqnac et al. (125) (117 ml/min) for CAD patients using the thermodilution method. It is possible that there is a positional difference in CSBF since ventricular volume would be smaller in the upright position (73) thus reducing $M\dot{V}O_2$ and CBF. Kitamura et al. (41) postulated this difference when comparing their data obtained in the upright position to that of Holmberg et al. (68) for the supine position.

Several studies (28, 51, 68) have failed to show any significant difference in resting CBF between CAD patients and normals. Klocke (83) attributes this to the afforementioned methodological weaknesses of the inert gas techniques and to the fact that the thermodilution technique which, by measuring absolute flow, does not take into account an increased myocardial mass often present in CAD patients. In heavy supine exercise Holmberg et al. (68) using the Xenon-133 clearance technique demonstrated smaller increases in coronary flow in patients with significant coronary obstructions (220%) as compared to those without obstruction (270%). Bertrand et al. (9) measured CSBF increases averaging 440% over resting thermodilution values with intense supine exercise in normal subjects and Kitamura et al. (82) reported an increase of 331% in nitrous oxide determined coronary flow during submaximal upright exercise in young normal subjects. Our patients with angina pectoris were only able to double CSBF during upright exercise.

In normal subjects increment of coronary blood flow has been found to contribute almost exclusively for the augmentation of $M\dot{V}O_2$ when exercise intensities ranged between one to three times the energy required at rest (88, 90, 104). At much higher exercise intensities, contrasting results have been reported. Some (82, 95) have found a significant widening of art-csO_2 difference and others (9, 68, 90) have reported similar values for art-csO_2 difference between their resting and exercise values. However, in patients with CAD, it has been a general finding that art-csO_2 difference exhibited a significantly greater increase during mild and/or severe exercise compared to the resting condition (68, 90). In our subjects, a great variation in resting values was observed between subjects confirming a characteristic that has been noted by all investigators who calculated the art-csO_2 difference (55, 62, 82, 88, 90, 104). From sitting rest to maximum exercise level before and after TRN the art-csO_2 difference was significantly increased by 19 and 17% respectively. Doll and Keul (35) in discussing reasons for a widened art-csO_2 difference at exercise in CAD patients believe that such adaptation is brought about by an increase in hemoglobin and by a fall in blood pH which shifted to the right the oxygen dissociation curve. Although our hemoglobin values tended to be slightly higher during exercise, the differences were not significant. However, the presence of similar $PcsO_2$ between rest and maximum exercise before and after TRN associated with a significant decrease of $ScsO_2$ in both conditions, could well be due at least partially to displacement of oxygen dissociation curve. It is also possible that with severe exercise, redistribution of 2.3-diphosphoglycerate has changed so that the affinity of hemoglobin for oxygen is decreased allowing more oxygen to be deliv-

ered at a given $Pcs0_2$ (95). More data are needed to decide if increasing oxygen extraction during exercise observed in CAD patients is abnormal. That such a result has not been generally observed in normal subjects during severe exercise is presently suggestive that this compensatory mechanism is closely related to CAD.

The major purpose of this investigation was to determine if the increased exercise tolerance of patients with angina pectoris after TRN could be explained on the basis of 1) decreased CBF requirement at any given workload and/or 2) an increase in CBF at the onset of angina. Significant increases of 38% in maximal workload on non-invasive tests and during the catheterization study are similar to those previously reported and attest to the effect of the training program (124).

The evidence obtained for peripheral modifications is that $M\dot{V}O_2$ and CSBF has been postulated to consistently decrease at a given workload after TRN as a result of lower HR and arterial BP and lower calculated indirect indices incorporing some of major factors determining $M\dot{V}O_2$ such as PRP, TP, and TTI (19, 24, 81, 135). The theorical basis that HR and the product of HR and arterial BP with the addition in some cases of SEP/beat are closely related to $M\dot{V}O_2$, has been verified in normal subjects during upright and supine dynamic exercise and in CAD patients in supine exercise. CBF and $M\dot{V}O_2$ measured from the nitrous oxide saturation method have been found to correlate well with PRP ($r = 0.87$ and $r = 0.90$), $\overline{PRP}$ ($r = 0.89$ and $r = 0.90$), TTI ($r = 0.83$ and $r = 0.77$) and HR alone ($r = 0.82$ and $r = 0.88$) in ten normal young subjects doing upright bicycle exercise at intensities corresponding to 53, 74 and 87% of the mean measured maximal HR (82). In similar subjects,

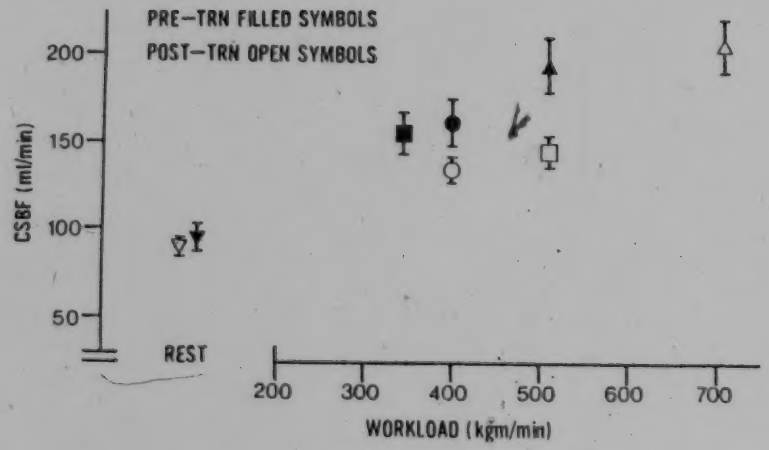
Bertrand et al. (9), using the thermodilution method for measuring CSBF and $M\dot{V}O_2$, found a coefficient of correlation of 0.87 for HR and 0.73 for TTI with CSBF during measurements made in supine position from rest through exhaustion. Similar correlation values were found with $M\dot{V}O_2$. In addition, Nelson et al. (95), combining data obtained in normal young subjects during dynamic upright exercise with and without propranolol, during combination of static and dynamic work, and during static work alone, have found that PRP correlated best with $M\dot{V}O_2$ ($r = 0.86$ and $r = 0.88$). These data were obtained from exercise in the supine position from rest through to near maximal workloads. Gobel et al. (53) have found a similar result with supine exercise between $M\dot{V}O_2$ and PRP ($r = 0.86$) in a group of CAD patients. Our results regarding measures of relationship between CSBF and $M\dot{V}O_2$ with the hemodynamic variables just mentioned are in agreement in that variables where SEP/beat are excluded give better correlation coefficients than those including this parameter. The correlations are similar when the patients are exercising in the upright position before and after TRN. These results are in accord with our present knowledge of $M\dot{V}O_2$ in that maintenance of tension is a relatively insignificant factor. As discussed by Kitamura et al. (82), with exercise the HR increases but the SEP/beat decreases as in inverse linear function of HR. Calculated mean differences for SEP/beat between sitting rest and maximal exercise have shown 19 and 18% decreases in SEP/beat before and after TRN respectively.

However, it was found that HR was not correlated better with CSBF ($r = 0.64$) than TTI ($r = 0.61$) and TP (0.67) before TRN. This finding is different than previously reported in normal subjects as well as in CAD patients. However, after TRN, HR had a higher correla-

tion coefficient with CSBF (r = 0.83) than $\overline{PRP}$ (r = 0.72) and PRP (r = 0.72). Inversely arterial BPs correlates better with CSBF (r = 0.60) before TRN than after TRN (r = 0.35).

That our patients were more severely disabled than those of Holmberg et al. (68) can be inferred from arteriography and clinical symptoms and this might be one reason explaining our lower coefficient of correlation for HR before TRN. It is evident that arterial BPs was as important a correlate as HR before TRN and that after TRN, the reverse occurred. The range HR was greater after TRN and this could have contributed to the improvement in the coefficient of correlation. A significant difference was obtained between pre and post TRN with a 67% change for HR before TRN and 103% change after TRN. In the presence of a such difference between the coefficient of correlation of HR with CSBF before and after TRN, and on the other hand considering the reproducibility of correlation coefficients when $\overline{PRP}$ was used, it appears important that indices including both HR and arterial BP be employed to estimate changes in CSBF or $M\dot{V}O_2$. TTI and TP correlated poorly with CSBF and $M\dot{V}O_2$ both before and after TRN. In the light of our data it seems reasonable to assume that changes in PRP and $\overline{PRP}$ during exercise can be interpreted as direct and proportional changes in CSBF of $M\dot{V}O_2$ which are independent of a training effect.

When mean values for CSBF for the various experimental conditions before and after TRN are plotted against workload (figure 3a) it is apparent that CSBF was not only lower after TRN at 400 kgm/min but also at 505 kgm/min. This latter workload corresponded to the angina threshold before TRN and to the mean level used to compare CSBF at an equal HR after TRN. These reduced CSBF values with TRN indicate that



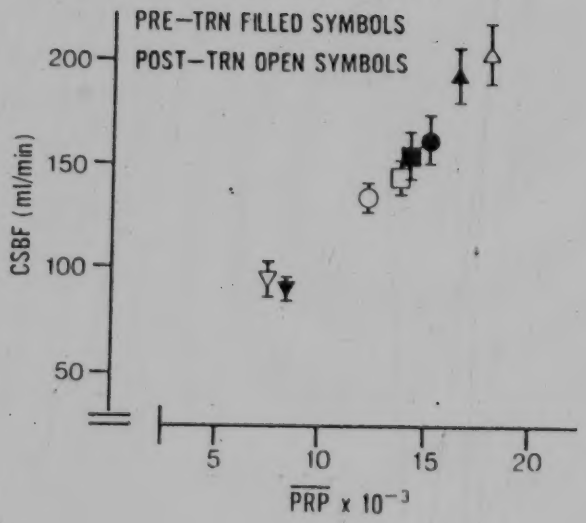


Fig. 3a. (left) Relationship of coronary sinus blood flow (CSBF) to workload pre and post training for the four experimental conditions: rest (inverted triangles), equivalent workload (circles), equivalent heart rate (squares) and maximal exercise (upright triangles). Values are mean ± standard error.

Fig. 3b. (right) Relationship of coronary sinus blood flow (CSBF) to the product of mean brachial artery pressure times heart rate ($\overline{PRP} \times 10^{-3}$) for the four experimental conditions pre and post training: rest (inverted triangles), equivalent workload (circles), equivalent heart rate (squares) and maximal exercise (upright triangles). Values are mean ± standard error.

the primary explanation for the increased exercise tolerance in these patients is a reduced CBF requirement for a workload which produced angina before TRN. Values for CVR, 0.82 mmHg/(ml/min) vs 0.67 mmHg/(ml/min) for pre and post TRN respectively, would also indicate that a vasodilatory reserve is still available at this workload post-training. As the workload was increased to approximately 700 kgm/min, CVR continued to decrease and CSBF increase to values not significantly different from those at the pre-training angina threshold. The reduction in CSBF and myocardial oxygen consumption for a given workload with training are related to decreases in adrenergic stimulation to the heart and systemic arteries as reflected by the lower HR, arterial BP and then calculated indirect indices such as $\overline{PRP}$, PRP, TTI and TP. The finding that arterial BP is decreased after TRN at similar workload has already been reported in studies done with CAD patients (19, 24, 33). However, at a given HR before and after TRN, no difference was observed in arterial BP. This result is also consistent with the fact that arterial BP is predominantly related to HR value as well as before than after TRN (93).

The exact mechanism for this reduced sympathetic output is not known. Based on exercise data from trained and untrained muscle groups, Clausen (20) postulates that the training bradycardia involves two components, one of which is present at rest and exercise and is related to changes in vagal tone. The other, related specifically to peripheral adaptive changes in the trained skeletal muscles, is present only in exercise and reflects a decrease in sympathetic drive. The ratio between the decrease in HR at rest and the decrease during exercise indicates the relative importance of the two components. The present data

(0.47) are in agreement with those of Clausen (0.41) for patients with angina pectoris, suggesting a more pronounced influence of peripheral adaptations (20). From data on rats (66) and normal subjects (56) following endurance training programs it has been hypothetized that the reduction in HR, muscle blood flow and peripheral vasoconstriction is mediated by increased skeletal muscle oxidative enzymatic capacity (20). In addition, at a given submaximal workload at pre and post TRN, our mean values for arterial blood LA and arterial catecholamine concentrations were significantly decreased after TRN, which could suggest that local adaptations of the trained muscles have contributed largely to change the autonomic stimulation of the heart (20). According to Hollozy (67) decreased arterial LA concentrations at a given workload after TRN could be explained by alterations of the oxidative enzymatic mechanism in trained muscles.

Given the low absolute training workloads of the angina patient alternative hypotheses could be warranted. In biopsies taken from the vastus medialus of our patients, Taylor et al. (132) did not find any systematic changes with training in oxidative enzymatic activity determined by qualitative histochemical staining (NADH diaphorase). However, significant hypertrophy of both fast and slow twitch fibres was present after bicycle ergometer training. There may be a mechanical metabolic stimulus involved in the afferent neural output from skeletal muscle and an enlargement of muscle fibres could permit a given workload to be performed using fewer motor units and/or more predominant slow twitch oxidative fibres with a reduction in this neural output and sympathetic drive.

The PRP has been shown to have a critical and relatively constant value at the onset of exercise angina pectoris (102, 105). Angina pectoris has been induced at the same PRP during exercise and right atrial pacing (8, 124). Several studies using progressive multi-stage exercise tests have demonstrated that following training patients often tolerate a higher PRP at the onset of angina pectoris (8, 20, 34, 124). This may be due to several factors. Firstly, the patient may tolerate a greater degree of ischemia before pain is perceived or reported. Detry and Bruce (34) found that the St-segment depression was significantly greater at symptom-limited maximal exercise after training. The exercise protocol employed may have an influence. A significant increase in PRP with training was observed in our patients on the non-invasive bicycle ergometer tests where the workload was progressively increased at two minute intervals. This was not the case during the catheterization studies where a longer period at a subangina level precede the onset of angina. Similarly, Gobel et al. (53) and Nordstrom et al. (96) studying the effect of lidoflazine noted increased PRP at angina on multi-stage treadmill tests but not during supine exercise during coronary sinus catheterization. Secondly, these may be concomitant changes in factors other than PRP, such as a reduction in contractile state or ventricular volume during maximal exercise. The former would imply an uncoupling of a parallel relationship between HR and contractile state at or near the onset of angina. When contractile state was influenced by propranolol, Jorgensen et al. (72) found increased SEP/beat for exercise of equal HR with versus without the drug. If the SEP/beat is used as an indirect index of contractile state the present data do not indicate this uncoupling since SEP/beat was similar before and after

training during exercise at the same HR and during maximal exercise. Measures of ventricular volume during upright exercise in patients with angina pectoris are warranted. That a change in these factors did not take place in this study is indicated by the linear relationship of mean values of $\overline{PRP}$ for all experimental conditions before and after training (figure 3b). Thirdly, TRN may result in changes in coronary blood flow distribution with reductions in "proximal steal" by parallel regions with lowered blood flow requirement post TRN leading to a higher maximum PRP at the angina threshold (20). Fourthly, is there an increase in the maximal myocardial blood flow and oxygen consumption with TRN? Whereas, TRN effects a two to four fold increase in skeletal muscle oxidative enzyme activity in normal subjects (96) no such adaptation has been noted for the heart of trained rats (97). Furthermore, the often quoted increases in collateral circulation in trained dogs (38) has not been demonstrated in man (26, 43). The present data are not adequate to answer this question fully.

Although, maximum CSBF and $\dot{M}VO_2$ were not significantly increased with TRN there appeared to be a subgroup of patients who reacted differently. Five of the seven patients whose maximum CSBF was higher after TRN also had higher maximum $\overline{PRP}$ values. On the other hand, only one of the four patients whose maximum CSBF decreased had an increase in maximum $\overline{PRP}$. Due to the length of time required for coronary sinus blood sampling complete data for $\dot{M}VO_2$ and art-csO_2 difference were available on seven subjects only four of whom belong to the group whose maximum CSBF increased with TRN. Three of these patients also had higher $\dot{M}VO_2$ and art-csO_2 differences after TRN.

CHAPTER VI

CONCLUSION

This study was designed primarily to evaluate the hemodynamic effects of training in patients with exertional angina pectoris and angiographically documented coronary artery disease. Experimental conditions for catheterization included sitting rest, an exercise at a given submaximal workload, a given submaximal heart rate and at the symptom-limited exercise capacity. Exercise was performed on a bicycle ergometer before and after training. On non-invasive multi-stage bicycle ergometer test, functional capacity and pressure-rate product were significantly higher after training suggesting a higher maximal coronary sinus blood flow or myocardial oxygen consumption. The assumption of a close relationship of indirect indices such as PRP, TP and TTI with coronary sinus blood flow was confirmed by pre and post-training data. However in both situations, TP and TTI which incorporate in their computations the systolic ejection period per beat were poorer correlates. It was also observed that pressure-rate product was better correlated with coronary sinus blood flow than heart rate or blood pressure alone both before and after training.

Exercise capacity during the catheterization evaluations was found to increase to a similar degree as during the non-invasive multi-stage tests. However the maximum pressure-rate product was not significantly different before and after training. Neither were the maximum

coronary sinus blood flow and myocardial oxygen consumption different with training. However in the majority of patients who increased their maximum pressure-rate product, the maximum coronary sinus blood flow was also higher after training, suggesting that although these patients were selected according to comparable criteria, some patients may respond differently to the training stimulus. However, it was clear that the primary factor contributing to the higher exercise capacity after training was a reduction of coronary blood flow requirement after training.

The coronary reserve of our patients was very limited with an ability to only double their coronary sinus blood flow at symptom-limited exercise. Arterio-coronary sinus oxygen difference contributed slightly to the increase of myocardial oxygen consumption from rest to maximum exercise before and after training (19 and 17% respectively). In the presence of similar $PcsO_2$ values at rest and at maximum exercise level, the higher arterio-coronary sinus oxygen difference was postulated by a displacement of the oxygen dissociation curve associated with a lower pH.

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APPENDIX A

INFORMED CONSENT

Je désire participer à un programme de conditionnement physique durant six (6) mois environ à raison de 3 sessions ou plus par semaine.

Le but de ce traitement est d'améliorer ma tolérance à l'effort et s'il y a lieu, de diminuer l'intensité et la fréquence de la douleur à la poitrine.

Afin de prescrire les activités adéquates et d'évaluer l'efficacité de ce programme, diverses épreuves d'effort sur bicyclette ergométrique seront effectuées avant et après le programme. Au cours de ces épreuves, l'intensité de l'effort sera augmentée graduellement jusqu'à ce que la fatique, l'essoufflement, la douleur à la poitrine ou d'autres symptômes m'indiquent d'arrêter.

L'effort pourrait être effectué 1) par les bras ou par les jambes, 2) précédé par un petit prélèvement du muscle par aiguille et 3) effectué après la mise en place d'un cathéter dans le coeur droit et une aiguille dans une artère du bras.

Il existe une possibilité que certains changements surviennent pendant ces épreuves ou lors des exercices du programme. Par exemple, une pression artérielle anormale, un étourdissement, les battements irréguliers du coeur, et très rarement (moins qu'une fois sur mille) une crise cardiaque.

Le risque de ces changements est minimisé par les examens préliminaires, les observations pendant, et la surveillance d'un médecin lors des épreuves d'effort et les exercices du programme. Le personnel entraîné et le matériel d'urgence sont disponibles dans le cas d'une situation inusitée.

La confidentialité des renseignements obtenus sera assurée et le dossier de chaque individu ne sera accessible qu'au personnel de recherche.

J'ai lu les renseignements qui précèdent et je consens à participer à ce programme.

Toute question que j'ai demandée a été expliquée à ma satisfaction.

Signé

_____

patient

_____

témoin

Date _____ _____

médecin

APPENDIX B

INDIVIDUAL DATA ON FUNCTIONAL

EXERCISE CAPACITY

INDIVIDUAL DATA ON FUNCTIONAL EXERCISE CAPACITY

Patient	Duration (min)			Workload (kgm/min)			Symptom limited		
	I†	II	III	I	II	III	I	II	III
GB	12	25	28	600	1125	1275	angina	angina	exhaustion
LB	6	9	12	450	525	600	angina	angina	angina
HD	8	8	7	450	450	450	angina	angina	angina
RF	9	10	15	525	525	750	angina	angina	angina
PG	10	15	18	525	750	825	angina	angina	angina
GL	15	15	16	600	665	725	exhaustion	St-segment*	St-segment
LG	9	13	17	525	675	825	angina	exhaustion	exhaustion
LR	13	15	16	675	750	750	angina	angina	angina
CS	15	18	20	750	825	900	angina	angina	exhaustion
MV	10	16	20	675	750	900	angina	angina	angina
YL	6	10	10	375	525	525	angina	angina	angina
$\bar{X}$	10	14	14	559	688	775			
S.D.	3	5	8	113	189	221			
n	11	11	11	11	11	11			

* Tests were stopped with a St-segment depression >5 mm.

† I = before training; II = mid-training; III = after training

(CONTINUED) INDIVIDUAL DATA ON FUNCTIONAL EXERCISE CAPACITY

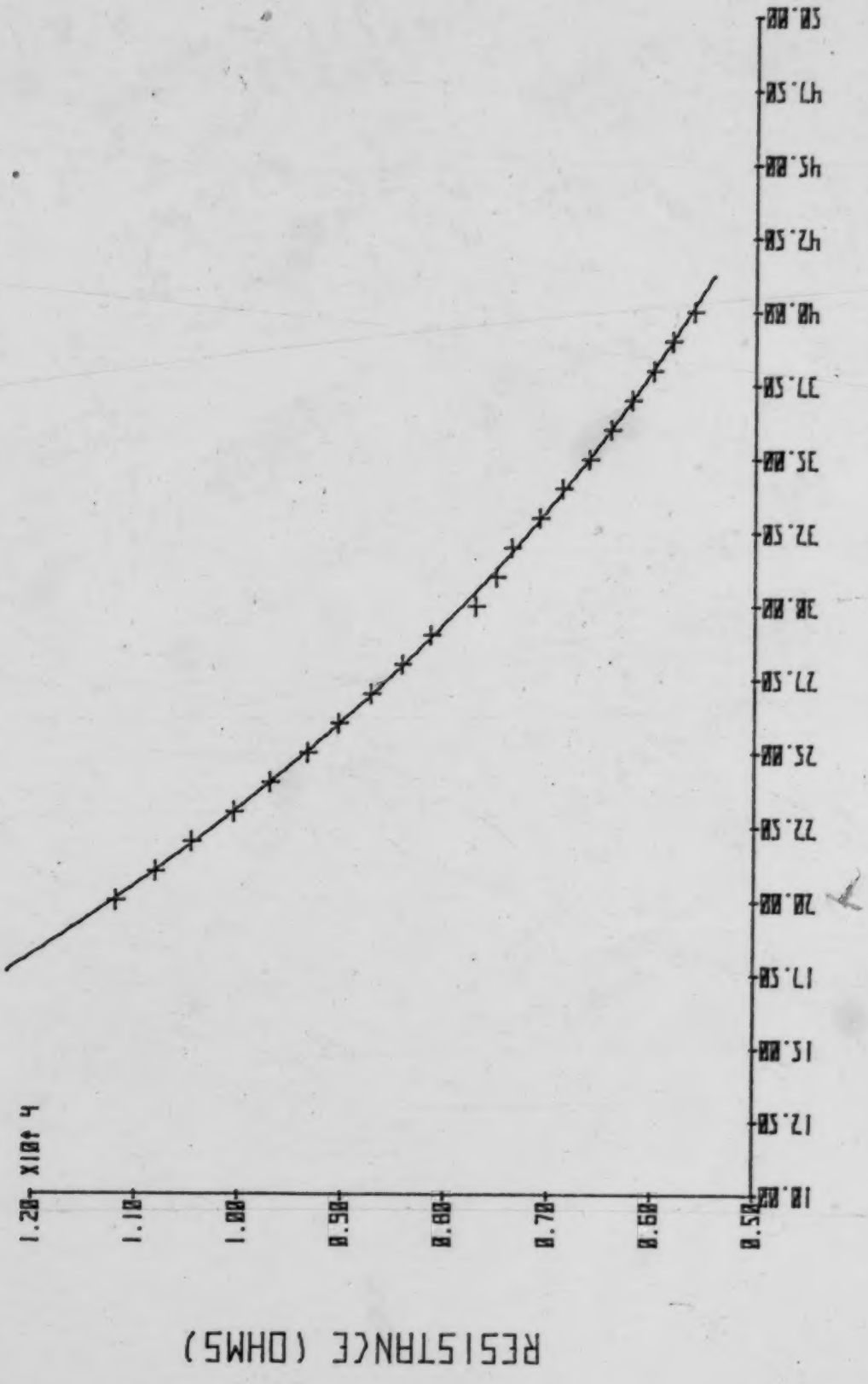
Patient	HR (beats/min)			BPs (mmHg)			PRP ($X\ 10^{-3}$)		
	I	II	III	I	II	III	I	II	III
GB	123	144	156	186	196	172	22.9	28.2	26.8
LB	126	129	142	230	252	254	29.0	32.5	36.1
HD	142	134	127	182	174	164	25.8	23.3	20.8
RF	106	102	117	182	164	222	19.3	16.7	26.0
PG	153	153	150	204	204	212	31.2	31.2	31.8
GL	111	116	136	192	182	202	21.3	21.1	27.5
LG	121	136	153	176	204	242	21.3	27.7	37.0
LR	138	139	150	184	184	196	25.4	25.6	29.4
CS	150	142	170	216	212	222	32.4	30.1	37.7
MV	140	129	153	196	198	224	20.4	25.5	34.3
YL	123	144	139	178	182	158	21.9	26.2	22.0
$\bar{X}$	130	133	145	193	196	206	24.6	26.2	30.0
S.D.	15	14	15	17	24	31	4.5	4.6	5.9
n	11	11	11	11	11	11	11	11	11

APPENDIX C

EXAMPLE OF CALIBRATION CURVE

IN THERMISTOR OF THERMO-

DILUTION CATHETER


TEMPERATURE (°C)
10.00
12.50
15.00
17.50
20.00
22.50
25.00
27.50
30.00
32.50
35.00
37.50
40.00
42.50
45.00
47.50
50.00
RESISTANCE (OHMS)
1.20
X10↑ 4
1.10
1.00
0.90
0.80
0.70
0.60
0.50

APPENDIX D

STANDARD ERROR OF MEASUREMENT (SEM)

AND ERROR IN % (E) OF CSBF,

LA, pH, PO_2 AND PCO_2

DETERMINATIONS

SEM AND E OF CSBF† DETERMINATIONS (ml/min)

Number of pair measurements		M_1 ‡	M_2
1		139	145
2		145	147
3		167	162
4		153	149
5		167	162
6		116	136
7		105	117
8		250	192
9		119	117
10		123	125
11		187	178
12		198	212
13		156	135
14		197	225
15		269	231
16		135	129
17		111	128
18		174	174
19		134	142
20		120	128
	$\overline{X}$	158	157
	S.D.	45	35

SEM = 13.6 ml

E = 8.6%

† Duplicate determinations taken at same $\overline{PRP}$ ($\pm 1 \times 10^{-3}$)

‡ M_1 = first measure; M_2 = second measure.

SEM AND E OF LA DETERMINATIONS (mg%)

Patient		Rest		Exercise†	
		M_1 ≠	M_2	M_1	M_2
GB	art	4.80	4.70	-	-
	cs	3.80	3.80	-	-
LB	art	7.45	7.55	14.32	14.62
	cs	7.65	7.65	9.52	9.42
HD	art	5.90	5.70	23.20	23.40
	cs	5.80	5.80	21.50	21.40
RF	art	7.50	7.43	20.10	20.55
	cs	6.45	6.52	14.62	15.00
PG	art	5.77	5.55	26.02	26.47
	cs	5.17	5.10	18.00	18.45
YL	art	4.90	5.00	36.56	36.86
	cs	4.90	4.90	39.34	39.34
GL	art	6.52	6.37	24.90	24.75
	cs	5.55	5.62	15.45	15.25
LR	art	4.10	4.15	57.04	55.87
	cs	3.40	3.40	47.34	47.72
CS	art	4.40	4.35	38.00	38.40
	cs	3.90	3.90	24.90	24.90
MV	art	9.70	9.90	23.20	23.20
	cs	5.90	5.80	-	-
	$\bar{X}$	5.67	5.66	26.71	26.80
	S.D.	1.56	1.59	12.82	12.67
	n	20	20	17	17
	SEM	0.067		0.314	
	E	1.2%		1.2%	

† Submaximal exercise level

≠ Duplicate determinations; M_1 = first measure; M_2 = second measure

SEM AND E OF pH, PO_2 (mmHg) and PCO_2 (mmHg) DETERMINATIONS

Sample† number	pH		PCO_2		PO_2	
	M_1 ǂ	M_2	M_1	M_2	M_1	M_2
1	7.582	7.589	29.4	29.3	131.4	129.8
2	7.409	7.423	40.8	40.3	71.6	69.3
3	7.495	7.487	22.8	24.3	173.0	173.0
4	7.444	7.450	38.0	36.4	191.7	192.8
5	7.389	7.387	38.1	38.3	89.2	91.3
6	7.457	7.453	42.4	42.4	147.8	145.7
7	7.523	7.526	28.7	27.9	202.8	199.7
8	7.524	7.523	26.7	26.6	200.8	196.3
9	7.159	7.150	75.7	77.6	294.5	312.2
10	7.477	7.475	23.0	23.0	109.5	108.5
11	7.415	7.415	32.0	32.0	141.7	143.7
12	7.483	7.474	37.3	37.9	165.2	163.5
13	7.482	7.480	32.1	32.6	203.4	202.4
14	7.205	7.202	68.5	67.8	89.8	90.9
15	7.496	7.493	32.8	33.1	146.9	149.2
16	7.431	7.429	36.6	37.0	43.2	53.5
17	7.405	7.297	41.5	41.0	103.8	104.1
18	7.438	7.445	35.3	35.6	116.5	116.8
19	7.392	7.390	35.8	36.5	96.3	94.4
20	7.444	7.445	42.4	42.6	98.5	101.0
$\bar{X}$	7.433	7.432	38.0	38.1	140.9	141.4
S.D.	0.099	0.101	13.1	13.1	58.8	60.9
SEM	0.004		0.45		3.12	
E	0.1%		1.2%		2.2%	

† Blood samples obtained in our laboratory.

ǂ Duplicate determinations; M_1 = first measure; M_2 = second measure.

APPENDIX E

INDIVIDUAL DATA RECORDING EACH TWO WEEKS DURING TRAINING

Mean workload (kgm/min) recorded each two weeks during training with legs bicycle upright exercise

Patient	WEEKS 2	4	6	8	10	12	14	16	18	20	22	24	26
GB	375	450	478	600	600	675	690	750	750	825	825	—	—
LB	300	375	435	450	495	—	525	525	525	—	—	—	—
HD	225	300	300	375	375	375	375	375	—	—	—	—	—
RF	375	450	450	450	450	—	450	437	525	450	—	450	450
PG	450	475	525	525	525	525	570	600	610	675	675	675	750
YL	300	300	330	375	375	375	420	450	450	—	—	—	—
JL	435	450	450	450	438	525	525	600	600	675	675	675	675
GL	360	450	450	525	525	525	525	525	525	525	525	525	525
LG	450	450	450	478	525	506	525	525	544	600	600	675	660
LR	488	450	450	450	525	—	525	488	—	—	—	—	—
CS	450	450	475	475	525	525	525	525	525	525	550	550	—
MV	450	525	525	557	600	600	600	600	675	675	—	—	—
RS	338	375	450	450	450	450	450	450	525	525	562	600	600
$\overline{X}$	384	423	444	474	493	508	516	527	569	608	630	593	610
S.D.	78	67	64	65	72	92	81	96	84	115	104	89	109
n	13	13	13	13	13	10	13	13	11	9	7	7	6

Mean heart rate (beats/min) recorded each two weeks during training with legs bicycle upright exercise

Patient	WEEKS												
	2	4	6	8	10	12	14	16	18	20	22	24	26
GB	91	106	101	107	112	108	114	115	121	124	137	—	—
LB	90	95	98	101	113*	—	129	127	133	—	—	—	—
HD	77	85	93	97	104	108	142*	143	—	—	—	—	—
RF	76	83	78	82	81	—	92*	100	106	98	—	103	108
PG	105	103	103	112	102	115	134*	134	141	135	140	144	157
YL	90	94	98	102	103	106	118	118	—	126	—	—	—
JL	113	112	110	101	105	114	118	126	109	114	111	113	118
GL	92	90	90	04	05	106	100	114*	121	125	112	119	108
LG	125	126	127	117	122	120	120	123	126	124	127	124	127
LR	153	132	145	142	164	—	155	155	—	—	—	—	—
CS	116	122	134	142	141	158	159	147	144	147	151	153	—
MV	95	94	92	95	97	97	108	116*	140	146	—	—	—
RS	98	99	97	96	97	95	98*	102	112	114	123	127	126
$\bar{X}$	102	103	105	107	110	113	122	125	125	125	129	126	124
S.D.	21	16	19	18	22	18	21	17	14	15	15	17	18
n	13	13	13	13	13	10	13	13	10	10	7	7	6

* Time where Inderal has been discontinued in these patients.

Mean workload (kgm/min) recorded each two weeks during training with arms bicycle exercise

Patient	WEEKS												
	2	4	6	8	10	12	14	16	18	20	22	24	26
LB	150	225	260	300	300	—	300	300	300	—	—	—	—
PG	270	300	315	356	375	375	395	425	450	450	375	375	450
YL	225	150	188	225	225	225	300	300	—	300	—	—	—
LR	300	300	300	300	375	—	375	375	—	—	—	—	—
CS	325	300	300	300	300	356	375	375	375	394	375	375	—
RS	300	375	375	375	375	375	483	450	450	525	525	525	525
$\bar{X}$	262	275	290	309	325	332	364	371	394	417	425	425	488
S.D.	64	77	62	53	61	72	54	62	72	95	87	87	53
n	6	6	6	6	6	4	6	6	4	4	3	3	2

Mean heart rate (beats/min) recorded each two weeks during training with arms bicycle exercise

Patient	WEEKS												
	2	4	6	8	10	12	14	16	18	20	22	24	26
LB	90	95	98	101	113*	—	129	127	133	—	—	—	—
PG	98	104	106	107	102	113	130	140	133	131	142	130	143
YL	93	99	93	103	106	110	108	114	—	115	—	—	—
LR	140	148	137	147	161	—	163	159	—	—	—	—	—
CS	128	133	125	121	123	146	156	152	149	154	149	152	—
RS	97	104	98	107	106	105	118	109	113	113	122	126	125
$\bar{X}$	108	114	110	114	119	118	134	134	132	128	138	136	129
S.D.	21	21	18	17	22	19	21	20	15	19	14	14	6
n	6	6	6	6	6	4	6	6	4	4	3	3	2

APPENDIX F

STATISTICAL ANALYSIS OF DATA OBTAINED AT FUNCTIONAL EXERCISE CAPACITY

a) ONE WAY ANALYSIS OF VARIANCE WITH REPEATED MEASURES FOR MAXIMUM TIME (min) DURING MULTI-STAGES BICYCLE ERGOMETER TEST

Summary Table:

Source	SS	DF	MS	F
Between S's	526.24	10		
Within S's	328.00	22		
Treatment	201.88	2	100.94	16.01**
Error	126.12	20	6.31	
Total	854.24	32		

** $F_{.99}(2,20) = 5.85$

b) NEWMAN-KEULS COMPARISON BETWEEN ORDERED MEANS FOR MAXIMUM TIME (min) DURING MULTI-STAGES BICYCLE ERGOMETER TEST

Ordered means	14	14	10
10	4**	4*	-
14	0	-	
14	-		

* Significant at α.05
** Significant at α.01

Critical values-$\alpha gr \sqrt{\text{MS error}/N}$

c) ONE WAY ANALYSIS OF VARIANCE FOR MAXIMUM PRP ($X\ 10^{-3}$) DURING MULTI-STAGES BICYCLE ERGOMETER TEST

Summary Table:

Source	SS	DF	MS	F
Between S's	526.56	10		
Within S's	763.88	22		
Treatment	164.36	2	82.18	6.93**
Error	237.32	20	11.87	
Total	928.23	32		

** $F_{.99}\ (2,20) = 5.85$

d) NEWMAN-KEULS COMPARISON BETWEEN ORDERED MEANS FOR MAXIMUM PRP ($X\ 10^{-3}$) DURING MULTI-STAGES BICYCLE ERGOMETER TEST

Ordered means	30.0	26.2	24.6
24.6	5.4**	1.6	-
26.2	3.8*	-	
30.0	-		

* Significant at $\alpha.05$
** Significant at $\alpha.01$

Critical values $= \alpha gr \sqrt{MS\ error/N}$

e) ONE WAY ANALYSIS OF VARIANCE FOR MAXIMUM WORKLOAD (kgm/min) DURING MULTI-STAGES BICYCLE ERGOMETER TEST

Summary Table:

Source	SS	DF	MS	F
Between S's	780,371.80	10		
Within S's	454,066.67	22		
Treatment	259,528.79	2	129,764.39	13.34**
Error	194,537.88	20	9,726.89	
Total	1,234,437.88	32		

** $F_{.99}$ (2,20) = 5.85

f) NEWMAN-KEULS COMPARISON BETWEEN ORDERED MEANS FOR MAXIMUM WORKLOAD (kgm/min) DURING MULTI-STAGES BICYCLE ERGOMETER TEST

Ordered means	775	688	559
559	216**	129**	-
688	87		
775			

** Significant at $\alpha.01$ Critical values = $\alpha gr \sqrt{MS\ error/N}$

g) ONE WAY ANALYSIS OF VARIANCE WITH REPEATED MEASURES FOR MAXIMUM HR (beats/min) DURING MULTI-STAGES BICYCLE ERGOMETER TEST

Summary Table:

Source	SS	DF	MS	F
Between S's	5,022.24	10		
Within S's	2,838.66	22		
Treatment	1,286.36	2	643.18	8.29**
Error	1,552.30	20	77.61	
Total	7,860.91	32		

** $F_{.99}$ (2,20) = 5.85

h) NEWMAN-KEULS COMPARISON BETWEEN ORDERED MEANS FOR MAXIMUM HR (beats/min) DURING MULTI-STAGES BICYCLE ERGOMETER TEST

Ordered means	145	133	130
130	15**	3	-
133	12**	-	
145	-		

** Significant at α.01 Critical values = $\alpha gr \sqrt{MS\ error/N}$

i) ONE WAY ANALYSIS OF VARIANCE WITH REPEATED MEASURES FOR MAXIMUM BPs (mmHg) DURING MULTI-STAGES BICYCLE ERGOMETER TEST

Summary Table:

Source	SS	DF	MS	F
Between S's	13,358.30	10		
Within S's	5,973.33	22		
Treatment	4,934.06	2	519.64	2.11
Error	1,039.27	20	246.7	
Total	19,331.64	32		

$F_{.95}(2,20) = 3.49$

APPENDIX G

INDIVIDUAL ANTHROPOMETRIC, HEMODYNAMIC AND HEMATOLOGIC DATA USED IN COMPUTATIONAL STATISTIC FOR THE EFFECTS TRAINING IN THE FOUR EXPERIMENTAL CONDITIONS

Anthropometric and respiratory functions data

Patient		Weight (kg)	VC (liter)	FEV_1 (liter)	FEV_1/CV (%)	Σ of 4 skinfold thickness (mm)
GB	I	64.2	4.2	3.2	76.2	59.5
	II	65.4	4.5	3.6	85.7	-
LB	I	76.4	4.0	3.6	90.0	71.5
	II	78.0	4.3	3.7	86.0	62.0
HD	I	66.0	-	-	-	61.5
	II	66.2	-	-	-	58.0
RF	I	79.0	3.4	3.0	88.2	68.5
	II	78.7	3.5	3.1	88.6	60.5
PG	I	66.5	4.9	4.4	89.8	40.0
	II	65.1	5.1	4.5	88.2	38.5
YL	I	75.7	3.6	3.2	88.9	73.6
	II	72.5	3.5	3.2	91.4	54.0
JL	I	63.5	3.6	2.6	72.2	20.0
	II	60.5	3.6	2.6	72.2	21.0
GL	I	82.4	3.5	2.6	74.3	90.5
	II	79.0	-	-	-	64.9
LG	I	56.5	4.8	3.0	62.5	22.5
	II	57.0	4.5	2.9	64.4	24.0
LR	I	58.0	4.3	3.7	86.0	20.5
	II	60.5	4.3	3.9	90.7	26.0
CS	I	66.0	4.1	3.8	92.7	32.0
	II	66.0	4.0	3.7	92.5	36.0
MV	I	69.0	-	-	-	54.0
	II	71.0	-	-	-	54.0
$\bar{X}$	I	68.0	4.1	3.4	82.9	50.4
S.D.	II	8.0	0.5	0.5	10.3	24.7
$\bar{X}$	I	68.0	4.1	3.5	84.4	45.4
S.D.	II	7.0	0.5	0.6	9.6	10.6

Hemodynamic data at sitting rest

Patient	HR† (beats/min)		HR (beats/min)		BPs (mmHg)		BPd (mmHg)		BPm†(mmHg)		BPm (mmHg)	
	I‡	II	I	II	I	II	I	II	I	II	I	II
GB	74	71	74	78	125	138	80	90	117	97	118	103
LB	77	75	80	69	179	178	89	96	135	144	140	-
HD	73	68	71	68	153	132	91	82	120	103	117	108
RF	72	77	76	70	161	137	76	71	98	103	107	93
PG	100	68	103	69	136	145	87	87	106	109	106	105
YL	86	78	84	82	174	151	106	100	132	125	134	128
GL	77	70	77	67	151	121	91	74	117	97	118	103
LR	71	63	71	66	125	119	69	68	87	92	85	93
CS	73	70	73	70	144	128	75	82	92	96	99	99
MV	73	63	79	61	141	138	92	85	113	103	114	112
$\bar{X}$	78	70	79	70	149	139	86	84	112	107	114	105
S.D.	9	5	9	6	19	17	11	10	16	16	16	11
n	10	10	10	10	10	10	10	10	10	10	10	9

† data taken during CSBF determination

‡ I = before training; II = after training

(Continued) Hemodynamic data at sitting rest

Patient	$\overline{CSP}$ (mmHg)		PRP ($\times 10^{-3}$)		$\overline{PRP}^{\dagger}$ ($\times 10^{-3}$)		$\overline{PRP}$ ($\times 10^{-3}$)		TP ($\times 10^{-3}$)		TTI ($\times 10^{-3}$)	
	I	II	I	II	I	II	I	II	I	II	I	II
GB	3	2	9.2	10.7	6.9	6.9	7.6	8.1	21.2	26.8	19.4	26.4
LB	1	0	14.4	12.4	10.4	10.9	11.2	-	33.8	33.5	30.8	31.9
HD	3	3	10.8	9.0	8.7	7.0	8.2	7.4	28.4	24.4	26.3	22.4
RF	5	6	12.2	9.6	7.0	7.9	8.1	6.5	35.9	26.3	32.5	24.2
PG	-	2	14.0	10.0	10.0	7.4	11.0	7.2	30.0	26.3	28.4	24.3
YL	4	8	14.6	12.3	11.4	9.8	11.3	10.5	36.1	28.3	32.5	26.4
GL	9	3	11.7	8.2	9.0	6.8	11.7	8.2	29.1	20.5	27.0	20.0
LR	0	-	8.9	7.8	6.2	5.8	6.1	6.1	22.3	19.8	18.3	17.7
CS	2	0	10.5	10.7	6.7	6.4	7.3	8.3	28.4	24.3	21.9	21.4
MV	6	5	11.2	9.9	8.2	6.5	9.1	6.9	29.8	26.6	28.3	25.8
$\overline{X}$	3	3	11.8	10.1	8.4	7.5	9.2	7.7	29.5	25.7	26.5	24.1
S.D.	3	3	2.1	1.5	1.8	1.6	2.0	1.3	5.0	3.9	5.1	4.0
n	7	7	10	10	10	10	10	9	10	10	10	10

(Continued) Hemodynamic data at sitting rest

Patient	SEP (sec)		CSBF (ml/min)		$M\dot{V}O_2$ (ml/min)		CVR (mmHg/(ml/min))		art-csO_2 (ml/100 ml)		mean BPs (mmHg)	
	I	II	I	II	I	II	I	II	I	II	I	II
GB	.23	.25	74	81	7.7	7.2	1.26	1.18	10.43	8.88	114	136
LB	.23	.27	109	112	11.7	15.6	1.22	1.28	10.76	13.86	163	170
HD	.26	.27	87	78	8.0	8.3	1.33	1.28	9.10	10.53	142	122
RF	.30	.27	104	83	12.0	9.5	0.90	1.17	11.75	11.52	146	126
PG	.22	.26	115	117	10.4	11.4	0.90	0.92	9.05	9.74	129	135
YL	.25	.23	139	97	20.4	11.9	0.93	1.19	14.65	12.22	156	141
GL	.25	.25	114	105	15.0	13.1	0.95	0.90	13.14	12.51	143	118
LR	.25	.25	79	88	8.1	9.3	1.12	1.05	10.45	10.60	103	106
CS	.27	.23	74	78	7.2	9.8	1.21	1.23	9.73	12.61	116	113
MV	.27	.28	58	63	6.5	5.9	1.86	1.55	11.29	9.33	134	151
$\bar{X}$	.25	.26	95	90	10.7	10.2	1.17	1.18	11.04	11.18	135	132
S.D.	.02	.02	25	17	4.3	2.9	.29	.19	1.77	1.62	19	19
n	10	10	10	10	10	10	10	10	10	10	10	10

Hemodynamic data at an equivalent submaximal workload (~400 kgm/min)

Patient	Workload		HR† (beats/min)		HR (beats/min)		BPs (mmHg)		BPd (mmHg)		BPm†(mmHg)		BPm (mmHg)	
	I‡	II	I	II	I	II	I	II	I	II	I	II	I	II
LB	350	350	119	105	125	105	241	243	116	117	177	167	171	172
HD	300	300	119	93	123	101	171	151	96	85	124	117	129	115
RF	300	300	98	88	97	91	177	144	70	66	121	94	114	105
PG	425	450	148	111	153	112	163	160	90	78	116	118	118	109
YL	275	275	118	99	117	106	176	172	103	101	133	132	138	137
GL	475	475	112	100	113	98	184	162	89	76	125	115	128	106
LR	450	475	114	116	112	115	173	177	69	78	115	112	113	112
CS	525	550	129	123	137	120	181	156	77	67	110	108	100	103
MV	450	450	125	94	129	100	154	150	87	80	116	107	118	115
$\bar{X}$	394	403	120	103	123	105	180	168	89	83	126	119	125	119
S.D.	90	98	14	11	16	9	25	30	15	16	20	21	20	22
n	9	9	9	9	9	9	9	9	9	9	9	9	9	9

† Data taken during CSBF determination

‡ I = before training; II = after training

(Continued) Hemodynamic data at an equivalent submaximal workload(~400 kgm/min)

Patient	$\overline{CSP}$ (mmHg)		PRP ($X\ 10^{-3}$)		$\overline{PRP}^{\dagger}$ ($X\ 10^{-3}$)		$\overline{PRP}$ ($X\ 10^{-3}$)		TP ($X\ 10^{-3}$)		TTI ($X\ 10^{-3}$)	
	I[†]	II	I	II	I	II	I	II	I	II	I	II
LB	2	13	30.0	25.6	21.1	17.6	21.3	18.1	77.8	74.0	71.9	65.8
HD	4	4	21.1	15.3	14.8	10.9	15.9	11.6	45.8	39.4	40.6	33.3
RF	6	10	17.3	13.3	11.9	8.3	11.1	9.6	45.1	37.2	40.4	38.1
PG	-	4	24.9	18.1	17.2	13.3	18.0	12.3	43.6	45.0	36.2	34.2
YL	5	7	20.5	18.1	15.6	13.2	16.1	14.5	44.9	45.4	41.8	42.2
GL	8	4	20.7	15.8	14.2	11.3	14.5	10.3	48.2	37.8	42.4	33.2
LR	3	0	19.3	20.4	13.2	12.9	12.6	12.9	46.1	47.7	39.4	39.1
CS	2	3	24.8	18.8	14.2	13.2	13.6	12.4	51.9	47.3	38.6	32.7
MV	7	8	19.9	15.1	14.5	10.1	15.3	11.5	45.6	39.1	44.9	35.7
$\overline{X}$	5	6	22.1	17.8	15.2	12.3	15.4	12.6	49.9	45.9	44.0	39.4
S.D.	2	4	3.8	3.7	2.7	2.6	3.0	2.5	10.7	11.3	10.7	10.4
n	8	8	9	9	9	9	9	9	9	9	9	9

(Continued) Hemodynamic data at an equivalent submaximal workload (~400 kgm/min)

Patient	SEP (sec)		CSBF (ml/min)		$M\dot{V}O_2$ (ml/min)		CVR (mmHg/(ml/min))		art-csO_2 (ml/100 ml)		mean BPs (mmHg)	
	I	II	I	II	I	II	I	II	I	II	I	II
LB	.26	.29	198	124	26.6	14.5	0.88	1.25	13.43	11.65	223	216
HD	.22	.26	138	117	14.0	13.3	0.87	0.97	10.13	11.40	151	128
RF	.26	.28	150	138	17.1	17.1	0.76	0.60	11.38	12.40	159	146
PG	.18	.25	238	174	23.4	22.2	0.50	0.66	9.84	12.79	135	123
YL	.22	.25	150	117	23.5	17.1	0.86	1.07	15.69	14.62	165	160
GL	.23	.24	165	132	27.0	20.1	0.70	0.84	15.46	15.30	163	138
LR	.24	.23	140	161	16.6	20.1	0.81	0.69	11.81	12.45	115	112
CS	.21	.20	167	144	19.6	19.7	0.64	0.73	11.74	13.67	135	136
MV	.23	.26	119	111	13.4	11.2	0.92	0.89	11.29	10.05	151	137
$\bar{X}$	.23	.25	163	138	20.1	17.3	0.77	0.86	12.31	12.70	155	144
S.D.	.02	.03	36	21	5.2	3.6	0.14	0.21	2.12	1.63	30	30
n	9	9	9	9	9	9	9	9	9	9	9	9

Hemodynamic data at an equivalent submaximal HR (~114 beats/min)

Patient	HR† (beats/min)		HR (beats/min)		BPs (mmHg)		BPd (mmHg)		BPm† (mmHg)		BPm (mmHg)	
	I‡	II	I	II	I	II	I	II	I	II	I	II
LB	104	105	104	106	239	243	121	118	173	168	169	172
RF	98	103	98	105	175	138	70	50	115	96	108	96
PG	135	130	134	134	161	181	91	89	115	122	115	129
YL	115	113	117	119	173	183	105	100	135	143	135	153
GL	102	103	104	99	156	156	78	76	115	110	119	104
LR	114	116	112	115	173	177	69	78	115	112	113	112
CS	123	123	127	120	152	156	68	67	104	108	97	103
MV	125	122	129	124	154	172	87	87	116	117	118	122
$\bar{X}$	114	114	116	115	173	176	86	83	124	122	122	124
S.D.	13	10	13	11	28	31	19	21	22	23	22	27
n	8	8	8	8	8	8	8	8	8	8	8	8

† Data obtained during CSBF determination

‡ I = before training; II = after training

(Continued) Hemodynamic data at an equivalent submaximal HR (~114 beats/min)

Patient	$\overline{CSP}$		PRP ($X\ 10^{-3}$)		$\overline{PRP}^{+}$ ($X\ 10^{-3}$)		$\overline{PRP}$ ($X\ 10^{-3}$)		TP ($X\ 10^{-3}$)		TTI ($X\ 10^{-3}$)	
	I	II	I	II	I	II	I	II	I	II	I	II
LB	1	12	24.7	25.6	18.1	17.6	17.4	18.1	65.7	74.0	59.8	65.8
RF	8	12	17.2	14.3	11.2	10.0	10.5	10.0	43.6	38.9	36.8	38.8
PG	-	5	21.6	24.3	15.7	15.9	15.6	17.2	40.0	59.4	33.0	48.9
YL	5	8	20.3	21.8	15.5	16.2	15.8	18.2	45.7	51.9	43.3	49.4
GL	8	4	16.4	15.5	11.7	11.0	12.5	10.3	36.9	36.8	36.0	31.3
LR	3	0	19.3	20.4	13.2	12.9	12.6	12.9	46.1	47.7	39.4	39.1
CS	2	3	19.4	18.8	12.8	13.2	12.4	12.4	37.8	37.7	32.8	32.7
MV	7	7	19.9	21.3	14.5	14.3	15.3	15.1	45.6	45.9	44.9	38.3
$\overline{X}$	5	7	19.9	20.3	14.1	13.9	14.0	14.3	45.2	49.0	40.7	43.0
S.D.	3	4	2.6	3.9	2.3	2.6	2.3	3.4	9.1	12.7	8.9	11.3
n	7	7	8	8	8	8	8	8	8	8	8	8

(Continued) Hemodynamic data at an equivalent submaximal HR (~114 beats/min)

Patient	SEP (sec)		CSBF (ml/min)		$\dot{M}VO_2$ (ml/min)		CVR (mmHg/(ml/min))		art-csO_2 (ml/100 ml)		mean BPs (mmHg)		Workload (kgm/min)	
	I	II	I	II	I	II	I	II	I	II	I	II	I	II
LB	.27	.29	183	124	20.4	14.4	0.94	1.25	11.16	11.65	218	216	225	350
RF	.25	.27	149	143	17.0	15.8	0.72	0.59	11.38	11.01	148	137	325	525
PG	.19	.24	221	195	22.5	23.7	0.53	0.60	10.62	12.16	132	150	300	575
YL	.22	.24	147	144	23.1	22.4	0.88	0.94	15.69	15.55	165	174	275	450
GL	.22	.24	149	129	25.2	19.7	0.71	0.83	16.77	15.30	152	132	275	495
LR	.24	.23	140	161	16.6	20.1	0.81	0.69	11.81	12.45	148	145	450	475
CS	.19	.20	136	144	15.8	19.7	0.75	0.73	11.64	13.67	134	136	450	550
MV	.23	.22	119	119	13.4	13.5	0.92	0.93	11.29	11.31	151	143	450	650
$\bar{X}$	.23	.24	156	145	19.2	18.7	0.78	0.82	12.55	12.89	156	154	344	506
S.D.	.03	.03	32	24	4.2	3.7	0.14	0.22	2.3	1.8	27	28	92	90
n	8	8	8	8	8	8	8	8	8	8	8	8	8	8

Hemodynamic data at maximum CSBF (ml/min)

Patient	HR† (beats/min)		HR (beats/min)		BPs (mmHg)		BPd (mmHg)		BPm† (mmHg)		BPm (mmHg)	
	I‡	II	I	II	I	II	I	II	I	II	I	II
GB	122	129	122	128	164	161	73	71	108	110	105	111
LB	117	121	115	122	237	254	108	121	182	156	156	167
HD	131	130	132	134	160	175	91	98	122	142	124	135
RF	115	117	119	117	205	181	82	57	122	111	120	112
PG	172	165	179	166	187	194	99	102	127	139	120	149
YL	147	128	-	128	-	196	-	111	146	151	-	154
GL	114	125	-	124	-	168	-	79	131	118	-	116
LG	131	129	135	130	-	180	-	88	134	131	-	127
LR	131	165	138	159	181	152	78	75	109	117	113	113
CS	129	171	137	170	181	181	77	81	110	120	100	125
MV	125	167	129	165	154	174	87	94	116	130	118	127
$\bar{X}$	130	141	134	140	184	183	87	89	128	130	120	130
S.D.	17	21	19	20	27	27	12	19	21	16	17	19
n	11	11	9	11	8	11	8	11	11	11	8	11

† Data taken during CSBF determination

‡ I = before training; II = after training

(Continued) Hemodynamic data at maximum CSBF (ml/min)

Patient	$\overline{CSP}$ (mmHg)		PRP ($\times 10^{-3}$)		$\overline{PRP^{\dagger}}$ ($\times 10^{-3}$)		$\overline{PRP}$ ($\times 10^{-3}$)		TP ($\times 10^{-3}$)		TTI ($\times 10^{-3}$)	
	I	II	I	II	I	II	I	II	I	II	I	II
GB	1	7	20.0	20.6	13.2	14.2	12.9	14.3	42.5	48.0	47.3	33.6
LB	3	16	27.4	30.9	21.3	18.9	18.1	20.3	64.3	81.0	56.3	69.4
HD	4	13	21.2	23.4	16.0	18.4	16.3	18.0	44.1	53.5	38.5	50.3
RF	7	8	24.4	21.2	14.1	13.0	14.3	13.1	55.5	55.6	42.3	48.2
PG	-	9	33.5	32.2	21.8	23.0	21.5	24.7	60.9	69.1	50.5	58.9
YL	-	7	-	25.1	21.5	19.3	-	19.8	-	57.9	-	55.6
GL	-	2	-	20.9	14.9	14.8	-	14.4	-	45.6	-	39.7
LG	-	2	-	23.3	17.5	16.8	-	16.5	-	52.3	-	49.1
LR	4	4	24.9	24.3	14.3	19.3	15.5	18.1	50.0	45.2	40.6	40.8
CS	2	8	24.8	30.7	14.2	20.2	13.6	21.2	51.9	56.2	38.6	47.1
MV	7	7	19.9	28.7	14.5	21.7	15.3	21.0	45.9	41.5	44.9	49.3
$\overline{X}$	7	8	24.5	25.6	16.7	18.2	15.9	18.3	51.9	55.1	44.9	49.3
S.D.	2	4	4.5	4.3	3.3	3.1	2.8	3.5	7.9	11.4	6.2	9.8
n	7	11	8	11	11	11	8	11	8	11	8	11

(Continued) Hemodynamic data at maximum CSBF (ml/min)

Patient	Workload (kgm/min)		SEP (sec)		CSBF (ml/min)		MVO_2 (ml/min)		CVR (mmHg/(ml/min))		art-csO_2 (ml/100 ml)		Mean BPs (mmHg)	
	I	II	I	II	I	II	I	II	I	II	I	II	I	II
GB	450	825	.21	.23	201	258	23.8	34.8	0.53	0.40	11.82	13.49	135	140
LB	375	450	.23	.26	233	169	31.3	19.7	0.77	0.83	13.43	11.63	208	218
HD	375	575	.21	.23	164	192	18.6	24.1	0.72	0.67	11.37	12.51	140	165
RF	600	675	.23	.26	204	234	-	29.3	0.60	0.44	-	12.53	155	167
PG	675	925	.18	.21	322	298	-	40.6	0.40	0.44	-	13.62	155	165
YL	450	450	-	.23	211	158	34.1	25.4	0.68	0.91	16.18	16.12	-	188
GL	500	725	-	.22	186	156	28.8	23.4	0.65	0.74	15.46	14.96	-	146
LG	650	700	-	.22	161	176	-	-	0.83	0.73	-	-	-	169
LR	525	650	.20	.19	177	258	23.6	29.8	0.60	0.44	13.39	11.56	148	138
CS	525	825	.21	.18	167	194	19.6	28.1	0.64	0.57	11.74	14.50	135	151
MV	450	950	.23	.10	119	166	13.2	-	0.92	0.74	11.29	-	151	154
$\bar{X}$	507	705	.21	.22	195	205	24.1	28.4	0.67	0.63	13.10	13.44	153	163
S.D.	101	170	.02	.03	52	49	7.0	6.3	0.14	0.18	1.89	1.55	24	23
n	11	11	8	11	11	11	8	9	11	11	8	9	8	11

Hematologic data at sitting rest

Patient	PaO_2 (mmHg)		$PcsO_2$ (mmHg)		CaO_2 (ml/100 ml)		$CcsO_2$ (ml/100 ml)		SaO_2 (%)		$ScsO_2$ (%)		Ht (%)	
	I†	II	I	II	I	II	I	II	I	II	I	II	I	II
GB	93.0	91.0	24.6	25.0	18.31	17.06	7.88	8.18	96.2	97.1	42.3	46.0	-	39
LB	105.0	95.0	24.0	41.7	19.58	18.56	8.82	4.70	98.0	96.8	43.0	24.9	42	41
HD	106.0	95.0	26.0	24.0	19.56	18.40	10.46	7.87	97.3	96.0	50.0	42.0	44	-
RF	85.0	90.5	24.0	23.5	19.36	19.68	4.61	8.16	95.0	95.9	40.0	40.6	44	46
PG	101.0	90.3	27.0	25.6	18.70	18.38	9.65	8.64	97.6	95.9	50.0	45.4	41	42
YL	104.0	92.4	20.0	22.0	21.39	19.40	6.74	7.18	97.8	96.5	31.0	35.7	47	44
GL	74.0	74.0	21.0	21.5	20.05	20.46	6.91	7.95	94.0	95.4	32.0	37.4	46	48
LR	103.6	103.0	21.4	22.0	18.79	18.65	8.34	8.05	98.0	98.0	42.3	36.0	42	-
CS	106.0	95.0	26.0	24.0	19.56	18.40	10.46	7.87	97.3	96.0	50.0	42.0	44	-
MV	105.0	94.0	24.0	28.0	19.71	18.76	8.42	9.43	98.0	97.2	43.0	51.0	41	-
$\bar{X}$	98.3	92.0	23.8	25.7	19.50	18.78	8.53	7.80	96.9	96.5	42.4	40.1	43	43
S.D.	10.9	7.3	2.3	5.9	0.85	0.91	1.33	1.23	1.4	0.8	6.8	7.2	2	3
n	10	10	10	10	10	10	10	10	10	10	10	10	9	6

†I= before training; II = after training

(Continued) Hematologic data at sitting rest

Patient	$PaCO_2$ (mmHg)		$PcsCO_2$ (mmHg)		pH (art)		pH (cs)		Hb (art) (gms)		Hb (cs) (gms)		Ht (%)	
	I	II	I	II	I	II	I	II	I	II	I	II	I	II
GB	34.7	32.0	44.3	44.0	7.40	7.44	7.37	7.40	14.1	13.8	13.8	13.1	-	39
LB	31.0	34.0	40.0	45.3	7.45	7.46	7.40	7.40	15.1	15.2	14.2	14.9	42	45
HD	29.2	36.0	29.4	47.0	7.41	7.40	7.41	7.38	14.9	14.2	15.5	13.9	46	-
RF	39.0	36.9	49.0	41.8	7.39	7.39	7.36	7.39	15.1	15.2	14.2	14.9	42	45
PG	31.0	36.6	42.0	45.0	7.43	7.40	7.38	7.37	14.2	14.2	14.3	14.1	41	41
YL	31.0	31.1	49.0	42.9	7.44	7.43	7.37	7.37	16.2	14.9	16.1	14.9	47	45
GL	31.0	34.0	41.0	46.2	7.41	7.42	7.36	7.41	15.8	15.9	16.0	15.9	47	49
LR	22.9	29.0	31.1	36.1	7.55	7.49	7.49	7.47	14.2	14.1	14.6	14.2	42	-
CS	34.4	38.7	41.5	49.4	7.42	7.44	7.39	7.40	14.4	13.8	14.4	13.9	42	41
MV	26.0	43.0	34.6	52.0	7.47	7.41	7.40	7.37	14.4	14.3	14.5	13.7	42	-
$\overline{X}$	31.0	35.1	40.2	45.0	7.44	7.43	7.39	7.40	14.8	14.6	14.7	14.4	43	44
S.D.	4.5	4.0	6.7	4.3	0.05	0.03	0.04	0.03	0.7	0.7	0.8	0.8	2	3
n	10	10	10	10	10	10	10	10	10	10	10	10	9	7

Hematologic data at an equivalent submaximal workload (~400 kgm/min)

Patient	PaO_2 (mmHg)		$PcsO_2$ (mmHg)		CaO_2 (ml/100 ml)		$CcsO_2$ (ml/100 ml)		SaO_2 (%)		$ScsO_2$ (%)		Ht (%)	
	I†	II	I	II	I	II	I	II	I	II	I	II	I	II
LB	88.0	95.0	21.0	23.3	20.12	19.14	6.69	7.49	96.8	96.3	32.0	38.3	44	43
HD	97.0	100.0	26.0	22.0	19.08	18.50	8.97	7.10	96.2	96.5	44.8	32.0	44	-
RF	93.0	86.0	23.0	21.9	18.77	19.00	7.39	6.60	96.6	94.4	38.0	33.3	-	45
PG	103.0	98.6	26.0	21.8	18.97	19.02	9.13	6.23	97.6	96.5	44.5	31.4	42	43
YL	101.0	93.0	18.0	19.6	21.19	19.99	5.50	5.37	97.5	96.2	24.7	26.5	47	45
GL	80.0	81.2	19.0	19.0	20.46	20.79	5.00	5.49	94.1	95.7	23.0	25.4	47	49
LR	91.5	90.0	22.7	24.0	18.07	19.13	6.26	6.68	94.9	94.5	30.5	33.0	42	-
CS	106.2	90.1	24.4	20.0	19.64	19.60	7.90	5.93	97.1	96.8	39.4	29.3	45	44
MV	95.0	92.0	25.0	26.0	19.31	18.44	8.02	8.39	96.0	96.9	41.0	43.5	43	-
$\bar{X}$	94.8	91.8	22.8	22.0	19.52	19.29	7.21	6.59	96.3	96.0	35.3	32.5	44	45
S.D.	8.1	5.9	2.9	2.2	0.97	0.74	1.45	0.97	1.2	0.9	8.1	5.6	2	2
n	9	9	9	9	9	9	9	9	9	9	9	9	8	6

†I = before training; II = after training

(Continued) Hematologic data at an equivalent submaximal workload (~400 kgm/min)

Patient	$PaCO_2$ (mmHg)		$PcsCO_2$ (mmHg)		pH (art)		pH (cs)		Hb (art) (gms)		Hb (art) (gms)		Ht (%)	
	I	II	I	II	I	II	I	II	I	II	I	II	I	II
LB	33.0	34.0	47.0	49.4	7.42	7.42	7.35	7.36	15.4	14.7	15.5	14.5	44	42
HD	31.0	33.0	42.0	53.0	7.38	7.37	7.34	7.31	14.8	14.2	15.2	13.9	46	-
RF	35.0	28.5	46.0	49.8	7.40	7.39	7.36	7.34	14.4	14.9	14.4	14.7	-	44
PG	29.0	34.6	42.0	51.2	7.40	7.39	7.35	7.32	14.4	14.6	15.2	14.7	43	44
YL	34.0	31.9	49.0	48.6	7.41	7.42	7.36	7.33	16.1	15.4	16.5	15.0	47	45
GL	31.0	32.2	46.5	52.0	7.37	7.38	7.31	7.33	16.1	16.1	16.2	16.0	46	49
LR	36.8	40.0	53.1	57.0	7.31	7.30	7.27	7.25	14.1	15.0	15.2	15.0	45	-
CS	31.8	37.2	45.0	55.5	7.40	7.39	7.34	7.35	15.1	15.0	15.1	15.0	45	44
MV	31.0	44.0	44.0	61.0	7.36	7.38	7.32	7.33	14.9	14.1	14.5	14.3	42	-
$\bar{X}$	32.5	35.0	46.1	53.1	7.38	7.38	7.33	7.32	15.0	14.9	15.3	14.8	45	45
S.D.	2.4	4.7	3.5	4.1	0.03	0.04	0.03	0.03	0.7	0.6	0.7	0.6	2	2
n	9	9	9	9	9	9	9	9	9	9	9	9	8	6

Hematologic data at an equivalent submaximal HR (~114 beats/min)

Patient	PaO_2 (mmHg)		$PcsO_2$ (mmHg)		CaO_2 (ml/100 ml)		$CcsO_2$ (ml/100 ml)		SaO_2 (%)		$ScsO_2$ (%)		Ht (%)	
	I†	II	I	II	I	II	I	II	I	II	I	II	I	II
LB	86.0	95.2	22.0	22.8	19.77	18.95	7.47	7.31	96.7	96.4	36.0	37.0	44	43
RF	93.0	88.2	23.0	25.8	18.77	19.28	7.39	8.27	96.6	95.2	38.0	41.7	-	46
PG	103.5	90.1	25.5	22.2	18.97	18.90	8.74	6.74	97.6	95.9	43.8	34.2	42	42
YL	101.0	93.0	18.0	17.7	21.19	19.60	5.50	4.05	97.5	96.2	24.7	20.7	47	44
GL	80.0	81.2	19.0	19.0	20.46	20.79	5.00	5.49	94.1	95.7	23.0	25.4	47	49
LR	91.5	90.0	22.7	24.0	18.07	19.13	6.26	6.68	94.9	94.5	30.5	33.0	42	-
CS	110.5	90.1	25.8	20.0	20.20	19.60	8.56	5.93	97.3	96.8	41.2	29.3	47	44
MV	95.0	106.0	25.0	25.0	19.31	19.34	8.02	8.03	96.0	97.5	41.0	40.5	43	-
$\bar{X}$	95.1	91.7	22.6	22.1	19.6	19.4	7.12	6.56	96.3	96.0	34.8	32.7	44	45
S.D.	9.8	7.1	2.9	2.9	1.0	0.6	1.4	1.4	1.3	0.9	7.8	7.3	2	2
n	8	8	8	8	8	8	8	8	8	8	8	8	7	6

†I = before training; II = after training

(Continued) Hematologic data at an equivalent submaximal HR (~114 beats/min)

Patient	$PaCO_2$ (mmHg)		$PcsCO_2$ (mmHg)		pH (art)		pH (cs)		Hb (art)		Hb (cs)		Ht (cs)	
	I	II	I	II	I	II	I	II	I	II	I	II	I	II
LB	32.0	34.2	44.5	49.1	7.43	7.42	7.37	7.36	15.3	14.6	15.5	14.7	44	43
RF	35.0	33.7	46.0	46.5	7.40	7.37	7.36	7.32	14.4	15.0	14.4	14.7	-	45
PG	29.0	35.9	42.0	47.7	7.40	7.39	7.35	7.34	14.4	14.6	15.2	14.6	43	43
YL	34.0	30.5	49.0	47.8	7.41	7.40	7.36	7.32	16.1	15.1	16.5	14.5	47	43
GL	31.0	32.2	46.5	52.2	7.37	7.38	7.31	7.33	16.1	16.1	16.1	16.0	46	49
LR	36.8	40.0	53.1	57.0	7.31	7.30	7.27	7.25	14.1	15.0	15.2	15.0	45	-
CS	34.3	37.2	46.5	55.5	7.35	7.39	7.31	7.35	15.5	15.0	15.4	15.0	46	44
MV	31.0	39.0	44.0	58.0	7.36	7.36	7.32	7.32	14.9	14.7	14.5	14.7	42	44
$\bar{X}$	32.9	35.3	46.4	51.7	7.38	7.38	7.33	7.32	15.1	15.0	15.3	14.9	45	44
S.D.	2.6	3.3	3.4	4.6	0.04	0.04	0.03	0.03	0.8	0.5	0.7	0.5	2	2
n	8	8	8	8	8	8	8	8	8	8	8	8	7	7

Hematologic data at maximum CSBF (ml/min)

Patient	PaO_2 (mmHg)		$PcsO_2$ (mmHg)		CaO_2 (ml/100 ml)		$CcsO_2$ (ml/100 ml)		SaO_2 (%)		$ScsO_2$ (%)		Ht (art) (%)	
	I†	II	I	II	I	II	I	II	I	II	I	II	I	II
GB	116.0	102.0	23.0	19.0	19.11	18.27	7.28	4.78	97.6	97.4	36.7	25.5	-	-
LB	88.0	95.3	21.0	22.3	20.12	18.76	6.69	7.13	96.8	96.5	32.0	35.7	44	43
HD	106.0	105.0	25.6	22.0	20.05	18.86	8.68	6.35	97.1	97.0	42.3	32.0	44	-
RF	-	86.0	-	23.3	-	19.13	-	6.60	-	94.5	-	33.3	-	46
PG	-	96.3	-	22.0	-	19.55	-	5.93	-	95.9	-	29.3	-	44
YL	105.0	96.5	19.0	17.0	21.60	19.66	5.42	3.54	97.5	96.5	24.5	18.1	47	44
GL	80.0	82.2	19.0	20.1	20.46	20.88	5.00	5.92	94.1	96.1	23.0	27.8	47	49
LR	87.7	89.0	21.9	27.0	18.76	19.00	5.37	7.44	94.5	94.5	26.9	37.0	43	-
CS	106.2	86.6	24.4	18.5	19.64	18.74	7.90	4.98	97.1	96.4	39.4	25.1	45	40
MV	95.0	-	25.0	-	19.31	-	8.02	-	96.0	-	41.0	-	42	-
$\bar{X}$	98.0	93.2	22.4	21.2	19.88	19.21	6.80	5.85	96.3	96.1	33.2	29.3	45	55
S.D.	12.2	7.7	2.6	3.0	0.89	0.76	1.40	1.24	1.4	1.0	7.7	6.0	2	3
n	8	9	8	9	8	9	8	9	8	9	8	9	7	6

† I = before training; II = after training

(Continued) Hematologic data at maximum CSBF (ml/min)

Patient	$PaCO_2$ (mmHg)		$PcsCO_2$ (mmHg)		pH (art)		pH (cs)		Hb (art) (gms)		Hb (cs) (gms)		Ht (%)	
	I	II	I	II	I	II	I	II	I	II	I	II	I	II
GB	33.2	31.0	43.4	45.0	7.38	7.38	7.34	7.33	14.5	13.9	14.7	13.9	-	-
LB	33.0	34.4	47.0	49.4	7.42	7.41	7.35	7.36	15.4	14.4	15.5	14.8	44	43
HD	28.2	27.0	42.4	46.0	7.40	7.41	7.33	7.32	14.5	13.9	14.7	13.9	45	-
RF	-	28.5	-	45.2	-	7.34	-	7.29	-	15.0	-	14.7	-	45
PG	-	32.6	-	49.5	-	7.34	-	7.28	-	15.1	-	15.0	-	45
YL	29.0	27.6	50.0	46.3	7.41	7.39	7.31	7.31	16.1	15.1	16.5	14.5	47	43
GL	31.0	28.0	46.5	48.4	7.37	7.40	7.31	7.32	16.1	16.1	16.1	15.8	46	-
LR	35.2	31.0	54.2	51.0	7.31	7.31	7.24	7.20	14.7	14.9	14.8	14.9	44	-
CS	31.8	27.9	45.0	48.0	7.40	7.37	7.34	7.29	15.1	15.0	15.1	14.7	45	-
MV	31.0	-	44.0	-	7.36	-	7.32	-	14.9	-	14.5	-	42	-
$\bar{X}$	31.6	29.8	46.6	47.6	7.38	7.37	7.32	7.30	15.2	14.8	15.2	14.7	45	44
S.D.	2.3	2.6	3.9	2.1	0.03	0.04	0.04	0.04	0.7	0.7	0.6	0.6	2	1
n	8	9	8	9	8	9	8	9	8	9	8	9	7	4

Arterial blood catecholamines data

Patients	Catecholamines (ng/ml)			
	Rest		Exercise	
	I†	II	I	II
GB	0.339	0.763	1.300	1.050
LB	0.612	0.594	1.080	0.909
HD	1.130	0.981	2.010	1.410
YL	0.840	0.661	0.927	0.847
LR	0.685	0.752	1.970	1.560
CS	0.592	0.818	1.900	1.720
MV	0.710	0.653	-	-
$\bar{X}$	0.702	0.746	1.501	1.249
S.D.	0.243	0.129	0.451	0.364
n	7	7	6	6

† I = before training; II = after training

Arterial blood lactates data

Patient	LACTATES (mg%)							
	A†		B		C		D	
	I‡	II	I	II	I	II	I	II
GB	4.7	4.4	32.9	18.6	-	-	32.9	31.5
LB	7.5	5.1	14.5	11.1	10.1	16.1	14.5	15.1
HD	5.8	-	22.6	16.3	-	-	22.6	45.2
RF	7.2	8.1	19.5	10.2	19.4	35.0	-	77.0
PG	5.7	4.8	26.7	11.1	16.1	16.1	-	54.0
YL	4.9	5.1	18.7	13.3	18.7	30.7	36.31	-
GL	6.3	7.0	24.2	22.6	14.5	22.6		45.3
LR	4.1	6.0	51.6	54.4	51.6	68.7	56.5	89.4
CS	4.4	4.1	32.8	28.8	38.2	28.3	32.8	81.0
MV	9.8	6.1	23.2	17.2	23.2	33.6	23.2	-
$\bar{X}$	5.9	5.6	26.7	20.3	24.0	31.4	31.3	54.8
S.D.	1.7	1.3	10.5	13.2	13.9	16.8	13.5	25.8
n	10	9	10	10	8	8	7	8

† A = sitting rest; B = equivalent submaximal workload; C = equivalent submaximal heart rate; D = maximum coronary sinus blood flow

‡ I = before training; II = after training

APPENDIX H

CODE SHEET AND INDIVIDUAL DATA USED IN COMPUTING CORRELATION COEFFICIENTS BEFORE AND AFTER TRAINING

CODE SHEET

Variable	Condition	Pre-TRN number†	Post-TRN number†
Levels of work (kgm/min)	- rest	1	151
	- exercise 1	2	152
	- exercise 2	3	153
	- exercise 3	4	154
	- exercise 4	5	155
	- exercise 5	6	156
	- max CSBF	7	157
HR (pressure) (beats/min)	- rest	8	158
	- exercise 1	9	159
	- exercise 2	10	160
	- exercise 3	11	161
	- exercise 4	12	162
	- exercise 5	13	163
	- max CSBF	14	164
HR (therm) (beats/min)	- rest	15	165
	- exercise 1	16	166
	- exercise 2	17	167
	- exercise 3	18	168
	- exercise 4	19	169
	- exercise 5	20	170
	- max CSBF	21	171
BPs (mmHg)	- rest	22	172
	- exercise 1	23	173
	- exercise 2	24	174
	- exercise 3	25	175
	- exercise 4	26	176
	- exercise 5	27	177
	- max CSBF	28	178
BPd (mmHg)	- rest	29	179
	- exercise 1	30	180
	- exercise 2	31	181
	- exercise 3	32	182
	- exercise 4	33	183
	- exercise 5	34	184
	- max CSBF	35	185

CODE SHEET (Continued)

Variable	Condition	Pre-TRN number†	Post-TRN number†
BPm (pressure) (mmHg)	- rest	36	186
	- exercise 1	37	187
	- exercise 2	38	188
	- exercise 3	39	189
	- exercise 4	40	190
	- exercise 5	41	191
	- max CSBF	42	192
BPm (therm) (mmHg)	- rest	43	193
	- exercise 1	44	194
	- exercise 2	45	195
	- exercise 3	46	196
	- exercise 4	47	197
	- exercise 5	48	198
	- max CSBF	49	199
$\overline{CSP}$ (mmHg)	- rest	50	200
	- exercise 1	51	201
	- exercise 2	52	202
	- exercise 3	53	203
	- exercise 4	54	204
	- exercise 5	55	205
	- max CSBF	56	206
mean BPs (mmHg)	- rest	57	207
	- exercise 1	58	208
	- exercise 2	59	209
	- exercise 3	60	210
	- exercise 4	61	211
	- exercise 5	62	212
	- max CSBF	63	213
SEP/beat (sec)	- rest	64	214
	- exercise 1	65	215
	- exercise 2	66	216
	- exercise 3	67	217
	- exercise 4	68	218
	- exercise 5	69	219
	- max CSBF	70	220

CODE SHEET (Continued)

Variable	Condition	Pre-TRN number†	Post-TRN number†
PRP	- rest	71	221
	- exercise 1	72	222
	- exercise 2	73	223
	- exercise 3	74	224
	- exercise 4	75	225
	- exercise 5	76	226
	- max CSBF	77	227
$\overline{PRP}$ (pressure)	- rest	78	228
	- exercise 1	79	229
	- exercise 2	80	230
	- exercise 3	81	231
	- exercise 4	82	232
	- exercise 5	83	233
	- max CSBF	84	234
$\overline{PRP}$ (therm)	- rest	85	235
	- exercise 1	86	236
	- exercise 2	87	237
	- exercise 3	88	238
	- exercise 4	89	239
	- exercise 5	90	240
	- max CSBF	91	241
TP	- rest	92	242
	- exercise 1	93	243
	- exercise 2	94	244
	- exercise 3	95	245
	- exercise 4	96	246
	- exercise 5	97	247
	- max CSBF	98	248
TTI	- rest	99	249
	- exercise 1	100	250
	- exercise 2	101	251
	- exercise 3	102	252
	- exercise 4	103	253
	- exercise 5	104	254
	- max CSBF	105	255

CODE SHEET (Continued)

Variable	Condition	Pre-TRN number†	Post-TRN number†
CSBF (ml/min)	- rest	106	256
	- exercise 1	107	257
	- exercise 2	108	258
	- exercise 3	109	259
	- exercise 4	110	260
	- exercise 5	111	261
	- max CSBF	112	262
$\dot{M}VO_2$ (ml/min)	- rest	113	263
	- exercise 1	114	264
	- exercise 2	115	265
	- exercise 3	116	266
	- exercise 4	117	267
	- exercise 5	118	268
	- max CSBF	119	269
CVR (mmHg/(ml/min)	- rest	120	270
	- exercise 1	121	271
	- exercise 2	122	272
	- exercise 3	123	273
	- exercise 4	124	274
	- exercise 5	125	275
	- max CSBF	126	276
art-csO_2 (ml/100 ml)	- rest	127	277
	- exercise 1	128	278
	- exercise 2	129	279
	- exercise 3	130	280
	- exercise 4	131	281
	- exercise 5	132	282
	- max CSBF	133	283

† digit 99.99 has been used to indicate no data.

PATIENT JL

	1	2	3	4	5	6	7	8	9	10
0	0.00	450.00	575.00	99.99	99.99	99.99	375.00	99.99	99.99	99.99
1	99.99	99.99	99.99	130.00	68.00	109.00	135.00	99.99	99.99	99.99
2	130.00	171.00	209.00	217.00	99.99	99.99	99.99	216.00	99.99	99.99
3	83.00	99.99	99.99	99.99	89.00	127.00	134.00	132.00	99.99	99.99
4	99.99	131.00	123.00	131.00	131.00	99.99	99.99	99.99	124.00	4.00
5	3.00	4.00	99.99	99.99	99.99	4.00	159.00	175.00	131.00	99.99
6	99.99	99.99	174.00	0.27	0.25	0.22	99.99	99.99	99.99	0.23
7	11.29	23.20	29.08	99.99	99.99	99.99	28.08	8.36	1.87	17.69
8	99.99	99.99	99.99	17.03	8.36	14.28	17.69	99.99	99.99	99.99
9	16.12	30.47	58.00	63.97	99.99	99.99	99.99	64.53	26.81	48.24
10	53.36	99.99	99.99	99.99	52.03	179.00	223.00	233.00	99.99	99.99
11	99.99	288.00	21.68	30.35	27.94	99.99	99.99	99.99	24.53	3.66
12	0.57	0.55	99.99	99.99	99.99	0.42	12.11	13.61	11.99	99.99
13	99.99	99.99	11.93	99.99	99.99	99.99	99.99	99.99	99.99	99.99
14	99.99	99.99	99.99	99.99	99.99	99.99	99.99	99.99	99.99	99.99
15	99.99	99.99	99.99	99.99	99.99	99.99	99.99	99.99	99.99	99.99
16	99.99	99.99	99.99	99.99	99.99	99.99	99.99	99.99	99.99	99.99
17	99.99	99.99	99.99	99.99	99.99	99.99	99.99	99.99	99.99	99.99
18	99.99	99.99	99.99	99.99	99.99	99.99	99.99	99.99	99.99	99.99
19	99.99	99.99	99.99	99.99	99.99	99.99	99.99	99.99	99.99	99.99
20	99.99	99.99	99.99	99.99	99.99	99.99	99.99	99.99	99.99	99.99
21	99.99	99.99	99.99	99.99	99.99	99.99	99.99	99.99	99.99	99.99
22	99.99	99.99	99.99	99.99	99.99	99.99	99.99	99.99	99.99	99.99
23	99.99	99.99	99.99	99.99	99.99	99.99	99.99	99.99	99.99	99.99
24	99.99	99.99	99.99	99.99	99.99	99.99	99.99	99.99	99.99	99.99
25	99.99	99.99	99.99	99.99	99.99	99.99	99.99	99.99	99.99	99.99
26	99.99	99.99	99.99	99.99	99.99	99.99	99.99	99.99	99.99	99.99
27	99.99	99.99	99.99	99.99	99.99	99.99	99.99	99.99	99.99	99.99
28	99.99	99.99	99.99	99.99	99.99	99.99	99.99	99.99	99.99	99.99
29	99.99	99.99	99.99	99.99	99.99	99.99	99.99	99.99	99.99	99.99

PATIENT 2B

	1	2	3	4	5	6	7	8	9	10
0	0.00	150.00	150.00	225.00	99.99	99.99	225.00	93.01	[illegible]	[illegible]
1	141.00	99.99	99.99	124.00	104.00	110.00	120.00	138.00	[illegible]	99.99
2	135.00	192.00	185.00	187.00	194.00	99.99	99.99	193.00	11[illegible].00	119.00
3	112.00	121.00	99.99	99.99	118.00	134.00	139.00	140.00	[illegible].00	99.99
4	99.99	139.00	121.00	114.00	137.00	154.00	99.99	99.99	138.00	6.00
5	6.00	8.00	8.00	99.99	99.99	8.00	152.00	156.00	162.00	178.00
6	99.99	99.99	190.00	0.21	0.22	0.21	0.21	99.99	99.99	0.22
7	17.86	19.06	22.07	27.35	99.99	99.99	23.93	12.46	14.32	16.52
8	19.60	99.99	99.99	17.24	12.58	12.54	16.44	21.25	99.99	99.99
9	18.63	37.50	41.92	46.34	57.44	99.99	99.99	52.65	25.69	35.25
10	40.14	52.71	99.99	99.99	51.83	130.00	154.00	182.00	182.00	99.99
11	99.99	209.00	11.66	16.89	19.97	22.06	99.99	99.99	20.14	0.88
12	0.70	0.71	0.72	99.99	99.99	0.62	8.97	10.97	10.97	11.07
13	99.99	99.99	11.07	99.99	99.99	99.99	99.99	99.99	99.99	99.99
14	99.99	99.99	99.99	99.99	99.99	99.99	99.99	99.99	99.99	99.99
15	99.99	99.99	99.99	99.99	99.99	99.99	99.99	99.99	99.99	99.99
16	99.99	99.99	99.99	99.99	99.99	99.99	99.99	99.99	99.99	99.99
17	99.99	99.99	99.99	99.99	99.99	99.99	99.99	99.99	99.99	99.99
18	99.99	99.99	99.99	99.99	99.99	99.99	99.99	99.99	99.99	99.99
19	99.99	99.99	99.99	99.99	99.99	99.99	99.99	99.99	99.99	99.99
20	99.99	99.99	99.99	99.99	99.99	99.99	99.99	99.99	99.99	99.99
21	99.99	99.99	99.99	99.99	99.99	99.99	99.99	99.99	99.99	99.99
22	99.99	99.99	99.99	99.99	99.99	99.99	99.99	99.99	99.99	99.99
23	99.99	99.99	99.99	99.99	99.99	99.99	99.99	99.99	99.99	99.99
24	99.99	99.99	99.99	99.99	99.99	99.99	99.99	99.99	99.99	99.99
25	99.99	99.99	99.99	99.99	99.99	99.99	99.99	99.99	99.99	99.99
26	99.99	99.99	99.99	99.99	99.99	99.99	99.99	99.99	99.99	99.99
27	99.99	99.99	99.99	99.99	99.99	99.99	99.99	99.99	99.99	99.99
28	99.99	99.99	99.99	99.99	99.99	99.99	99.99	99.99	99.99	99.99
29	99.99	99.99	99.99	99.99	99.99	99.99	99.99	99.99	99.99	99.99

PATIENT: 08

	1	2	3	4	5	6	7	8	9	10
0	0.00	500.00	450.00	575.00	99.99	99.99	525.00	73.00	[illegible]	[illegible]
1	150.00	99.99	99.99	137.00	73.00	111.00	123.00	144.00	99.99	99.99
2	129.00	144.00	193.00	152.00	179.00	99.99	99.99	181.00	73.00	73.00
3	68.00	77.00	99.99	99.99	77.00	99.00	112.00	97.00	112.00	99.99
4	99.99	100.00	92.00	109.00	104.00	109.00	99.99	99.99	113.00	2.00
5	4.00	2.00	1.00	99.99	99.99	2.00	116.00	150.00	134.00	134.00
6	99.99	99.99	135.00	0.27	0.22	0.19	0.21	99.99	99.99	0.21
7	10.51	21.81	19.30	26.85	99.99	99.99	24.30	7.00	12.66	12.00
8	16.80	99.99	99.99	13.70	6.72	12.10	12.79	15.70	99.99	99.99
9	14.19	28.38	47.98	36.68	56.39	99.99	99.99	52.07	32.86	37.39
10	32.33	42.21	99.99	99.99	38.34	74.00	116.00	136.00	123.00	99.99
11	99.99	167.00	7.20	13.50	15.83	14.81	99.99	99.99	14.81	1.23
12	0.91	0.75	0.90	99.99	99.99	0.65	9.73	11.64	11.64	12.34
13	99.99	99.99	11.74	99.99	99.99	99.99	99.99	99.99	99.99	99.99
14	99.99	99.99	99.99	99.99	99.99	99.99	99.99	99.99	99.99	99.99
15	0.00	550.00	700.00	99.99	99.99	99.99	825.00	70.00	120.00	138.00
16	99.99	99.99	99.99	170.00	70.00	123.00	140.00	99.99	99.99	99.99
17	171.00	123.00	156.00	184.00	99.99	99.99	99.99	181.00	82.00	67.00
18	80.00	99.99	99.99	99.99	81.00	99.00	103.00	126.00	99.99	99.99
19	99.99	125.00	96.00	108.00	123.00	99.99	99.99	99.99	120.00	0.00
20	3.00	5.00	99.99	99.99	99.99	8.00	113.00	136.00	160.00	99.99
21	99.99	99.99	151.00	0.23	0.20	0.21	99.99	99.99	99.99	0.19
22	8.96	18.72	25.39	99.99	99.99	99.99	30.77	6.93	12.36	17.39
23	99.99	99.99	99.99	21.25	6.72	13.28	17.22	99.99	99.99	99.99
24	20.52	20.61	37.44	53.32	99.99	99.99	99.99	55.39	10.19	32.64
25	46.37	99.99	99.99	99.99	46.21	78.00	144.00	184.00	99.99	99.99
26	99.99	194.00	9.84	19.68	25.32	99.99	99.99	99.99	20.13	1.23
27	0.73	0.64	99.99	99.99	99.99	0.58	12.61	13.67	11.76	99.99
28	99.99	99.99	14.50	99.99	99.99	99.99	99.99	99.99	99.99	99.99
29	99.99	99.99	99.99	99.99	99.99	99.09	99.99	99.99	99.99	99.99

PATIENT LG	1	2	3	4	5	6	7	8	9	10
0	99.99	225.00	225.00	450.00	450.00	99.99	650.00	99.99	100.00	100.00
1	118.00	118.00	99.99	135.00	99.99	97.00	102.00	113.00	121.00	99.99
2	131.00	99.99	114.00	105.00	99.99	99.99	99.99	99.99	99.99	79.00
3	77.00	99.99	99.99	99.99	99.99	99.99	93.00	88.00	120.00	125.00
4	99.99	99.99	99.99	96.00	86.00	134.00	124.00	99.99	134.00	0.00
5	0.00	0.00	0.00	0.00	0.00	0.00	99.99	113.00	102.00	99.99
6	99.99	99.99	99.99	99.99	0.25	0.25	0.22	0.21	99.99	99.99
7	99.99	11.51	11.13	99.99	99.99	99.99	99.99	99.99	3.39	3.33
8	15.10	14.75	99.99	99.99	99.99	9.31	8.77	15.14	16.00	99.99
9	17.55	99.99	28.79	27.83	99.99	99.99	99.99	99.99	99.99	26.53
10	27.03	99.99	99.99	99.99	99.99	99.99	93.00	111.00	156.00	105.00
11	99.99	161.00	99.99	99.99	99.99	99.99	99.99	99.99	99.99	99.99
12	1.03	0.77	0.86	0.92	99.99	0.83	99.99	99.99	99.99	99.99
13	99.99	99.99	99.99	99.99	99.99	99.99	99.99	99.99	99.99	99.99
14	99.99	99.99	99.99	99.99	99.99	99.99	99.99	99.99	99.99	99.99
15	99.99	99.99	99.99	99.99	99.99	600.00	700.00	99.99	99.99	99.99
16	99.99	99.99	119.00	130.00	99.99	99.99	99.99	99.99	99.99	119.00
17	129.00	99.99	99.99	99.99	99.99	99.99	171.00	180.00	99.99	99.99
18	99.99	99.99	99.99	80.00	88.00	99.99	99.99	99.99	99.99	99.99
19	129.00	127.00	99.99	99.99	99.99	99.99	99.99	124.00	131.00	99.99
20	99.99	99.99	99.99	99.99	2.00	2.00	99.99	99.99	99.99	99.99
21	99.99	165.00	169.00	99.99	99.99	99.99	99.99	99.99	0.24	0.22
22	99.99	99.99	99.99	99.99	99.99	20.35	23.40	99.99	99.99	99.99
23	99.99	99.99	15.35	16.51	99.99	99.99	99.99	99.99	99.99	14.76
24	16.90	99.99	99.99	99.99	99.99	99.99	48.84	51.48	99.99	99.99
25	99.99	99.99	99.99	47.12	48.33	99.99	99.99	99.99	99.99	99.99
26	154.00	176.00	99.99	99.99	99.99	99.99	99.99	99.99	99.99	99.99
27	99.99	99.99	99.99	99.99	0.79	0.73	99.99	99.99	99.99	99.99
28	99.99	99.99	99.99	99.99	99.99	99.99	99.99	99.99	99.99	99.99
29	99.99	99.99	99.99	99.99	99.99	99.99	99.99	99.99	99.99	99.99

PATIENT FF

	1	2	3	4	5	6	7	8	9	10
0	0.00	225.00	225.00	300.00	350.00	450.00	600.00	76.00	84.00	88.00
1	97.00	99.00	112.00	119.00	72.00	86.00	89.00	98.00	97.00	113.00
2	115.00	161.00	170.00	173.00	177.00	173.00	195.00	205.00	75.00	71.00
3	73.00	70.00	71.00	80.00	82.00	107.00	112.00	112.00	114.00	101.00
4	120.00	120.00	98.00	109.00	110.00	121.00	110.00	121.00	122.00	5.00
5	6.00	6.00	6.00	9.00	8.00	7.00	146.00	151.00	150.00	159.00
6	137.00	164.00	155.00	0.30	0.28	0.28	0.26	0.24	0.24	0.22
7	12.24	15.13	15.57	17.17	17.13	21.94	24.40	8.13	9.97	10.08
8	11.06	10.00	13.44	14.28	7.06	9.37	9.79	11.86	10.67	13.31
9	14.03	36.71	42.36	43.60	44.64	41.10	52.42	56.11	33.29	37.63
10	37.80	40.10	32.55	44.08	42.42	104.00	123.00	125.00	150.00	148.00
11	165.00	204.00	12.32	13.63	13.85	17.07	16.34	99.99	99.99	0.39
12	0.84	0.83	0.77	0.68	0.68	0.56	11.75	11.08	11.08	11.38
13	11.38	99.99	99.99	99.99	99.99	99.99	99.99	99.99	99.99	99.99
14	99.99	99.99	99.99	99.99	99.99	99.99	99.99	99.99	99.99	99.99
15	0.00	300.00	300.00	525.00	99.99	99.99	675.00	70.00	90.00	93.00
16	104.00	99.99	99.99	117.00	77.00	85.00	91.00	103.00	99.99	99.99
17	117.00	137.00	148.00	144.00	138.00	99.99	99.99	181.00	71.00	65.00
18	68.00	48.00	99.99	99.99	57.00	93.00	109.00	102.00	96.00	99.99
19	99.99	112.00	103.00	96.00	93.00	96.00	99.99	99.99	111.00	6.00
20	10.00	10.00	12.00	99.99	99.99	8.00	136.00	155.00	137.00	137.00
21	99.99	99.99	157.00	0.27	0.29	0.27	0.27	99.99	99.99	0.26
22	9.59	13.32	13.39	14.35	99.99	99.99	21.18	6.51	8.81	9.40
23	9.98	99.99	99.99	13.10	7.93	8.16	8.46	9.89	99.99	99.99
24	12.99	25.89	38.63	36.16	38.75	99.99	99.99	55.06	23.81	40.46
25	34.40	38.47	99.99	99.99	47.76	83.00	134.00	142.00	140.00	99.99
26	99.99	234.00	9.56	16.62	17.61	15.74	99.99	99.99	29.32	1.17
27	0.64	0.58	0.59	99.99	99.99	0.44	11.52	12.40	12.40	11.01
28	99.99	99.99	12.53	99.99	99.99	99.99	99.99	99.99	99.99	99.99
29	99.99	99.99	99.99	99.99	99.99	99.99	99.99	99.99	99.99	99.99

PATIENT: GL

	1	2	3	4	5	6	7	8	9	0
0	0.00	325.00	275.00	475.00	475.00	99.99	500.00	77.00	100.00	94.00
1	112.00	114.00	99.99	99.99	77.00	97.00	102.00	112.00	111.00	99.99
2	114.00	152.00	165.00	156.00	179.00	188.00	99.99	99.99	91.00	81.00
3	78.00	88.00	90.00	99.99	99.99	118.00	117.00	119.00	120.00	127.00
4	99.99	99.99	117.00	115.00	115.00	122.00	129.00	99.99	131.00	9.00
5	8.00	8.00	7.00	9.00	99.99	8.00	142.00	137.00	152.00	161.00
6	164.00	99.99	99.99	0.25	0.23	0.22	0.24	0.23	99.99	99.99
7	11.70	16.50	16.22	20.05	21.43	99.99	99.99	9.09	11.70	12.33
8	14.56	14.48	99.99	99.99	9.01	11.16	11.73	13.66	14.60	99.99
9	14.93	29.26	37.95	35.69	48.12	49.29	99.99	99.99	27.04	21.51
10	34.78	43.28	43.00	99.99	99.99	114.00	153.00	149.00	167.00	163.00
11	99.99	186.00	14.98	25.66	24.99	25.82	25.05	99.99	28.76	0.95
12	0.70	0.72	0.69	0.74	99.99	0.66	13.14	16.77	16.77	15.46
13	15.46	99.99	15.46	99.99	99.99	99.99	99.99	99.99	99.99	99.99
14	99.99	99.99	99.99	99.99	99.99	99.99	99.99	99.99	99.99	99.99
15	0.00	475.00	475.00	575.00	99.99	99.99	725.00	67.00	87.00	99.00
16	111.00	99.99	99.99	124.00	70.00	96.00	103.00	115.00	99.99	99.99
17	125.00	121.00	167.00	156.00	161.00	99.99	99.99	168.00	74.00	76.00
18	76.00	77.00	99.99	99.99	79.00	103.00	107.00	104.00	111.00	99.99
19	99.99	116.00	97.00	121.00	110.00	120.00	99.99	99.99	118.00	3.00
20	4.00	4.00	3.00	99.99	99.99	2.00	118.00	145.00	132.00	147.00
21	99.99	99.99	146.00	0.25	0.25	0.24	0.23	99.99	99.99	0.12
22	8.11	16.20	15.44	17.87	99.99	99.99	20.83	6.90	10.38	10.00
23	12.32	99.99	99.99	14.38	6.79	11.62	11.33	13.80	99.99	99.99
24	14.75	20.27	40.50	37.07	41.10	99.99	99.99	45.83	19.77	35.16
25	31.36	37.53	99.99	99.99	39.83	105.00	135.00	129.00	121.00	99.99
26	99.99	156.00	13.14	20.66	19.74	18.45	99.99	99.99	23.34	0.40
27	0.87	0.82	0.97	99.99	99.99	0.74	12.51	15.30	15.30	15.25
28	99.99	99.99	14.96	99.99	99.99	99.99	99.99	99.99	99.99	99.99
29	99.99	99.99	99.99	99.99	99.99	99.99	99.99	99.99	99.99	99.99

PATIENT: MV

	1	2	3	4	5	6	7	8	9	10
0	0.00	375.00	350.00	475.00	575.00	99.99	450.00	79.00	111.00	120.00
1	126.00	133.00	99.99	129.00	73.00	114.00	119.00	124.00	136.00	99.99
2	125.00	141.00	157.00	154.00	149.00	160.00	99.99	154.00	92.00	86.00
3	87,00	84.00	90.00	99.99	87.00	114.00	117.00	118.00	114.00	124.00
4	99.99	118.00	113.00	116.00	114.00	119.00	125.00	99.99	116.00	6.00
5	7.00	1.00	3.00	5.00	99.99	7.00	134.00	140.00	141.00	153.00
6	152.00	99.99	151.00	0.27	0.24	0.22	0.22	0.22	99.99	0.23
7	11.14	17.43	18.48	18.77	21.28	99.99	19.87	9.01	12.99	14.16
8	14.36	16.49	99.99	15.22	8.25	13.22	13.57	14.76	17.00	99.99
9	14.50	30.08	41.82	40.66	41.30	46.82	99.99	45.69	28.58	37.30
10	37.22	42.41	44.48	99.99	44.80	58.00	105.00	117.00	117.00	110.00
11	99.99	119.00	6.55	12.60	14.04	13.21	10.46	99.99	13.44	1.84
12	1.04	0.97	0.99	1.09	99.99	0.92	11.29	12.00	12.00	11.29
13	9.51	99.99	11.29	99.99	99.99	99.99	99.99	99.99	99.99	99.99
14	99.99	99.99	99.99	99.99	99.99	99.99	99.99	99.99	99.99	99.99
15	0.00	450.00	450.00	650.00	99.99	99.99	950.00	61.00	100.00	108.00
16	124.00	99.99	99.99	165.00	63.00	94.00	109.00	122.00	99.99	9.99
17	167.00	138.00	150.00	147.00	172.00	99.99	99.99	174.00	85.00	80.00
18	79.00	87.00	99.99	99.99	94.00	112.00	115.00	113.00	122.00	99.99
19	99.99	127.00	103.00	107.00	108.00	117.00	99.99	99.99	130.00	5.00
20	3.00	6.00	7.00	99.99	99.99	7.00	151.00	137.00	131.00	143.00
21	99.99	99.99	154.00	0.28	0.26	0.23	0.22	99.99	99.99	0.19
22	3.42	15.00	15.88	21.33	99.99	99.99	28.71	6.83	11.50	12.20
23	15.13	99.99	99.99	20.96	6.49	10.06	11.77	14.27	99.99	99.99
24	21.71	23.57	39.00	36.51	46.92	99.99	99.99	54.55	25.79	35.62
25	32.54	39.01	99.99	99.99	48.28	63.00	111.00	128.00	119.00	99.99
26	99.99	166.00	5.88	11.16	12.86	13.46	99.99	99.99	99.99	1.56
27	0.89	0.90	0.92	99.99	99.99	0.74	9.33	10.05	10.05	11.31
28	99.99	99.99	99.99	99.99	99.99	99.99	99.99	99.99	99.99	99.99
29	99.99	99.99	99.99	99.99	99.99	99.99	99.99	99.99	99.99	99.99

PATIENT LB

	1	2	3	4	5	6	7	8	9	10
0	0.00	225.00	225.00	350.00	325.00	99.99	375.00	80.00	103.00	104.00
1	125.00	118.00	99.99	115.00	77.00	104.00	105.00	119.00	123.00	99.99
2	117.00	179.00	237.00	242.00	241.00	248.00	99.99	237.00	89.00	119.00
3	123.00	116.00	117.00	99.99	108.00	140.00	170.00	167.00	171.00	180.00
4	99.99	156.00	135.00	176.00	170.00	177.00	181.00	99.99	182.00	1.00
5	1.00	1.00	2.00	9.00	99.99	3.00	163.00	220.00	217.00	223.00
6	228.00	99.99	208.00	0.23	0.27	0.26	0.26	0.25	99.99	0.23
7	14.32	24.41	25.17	30.13	29.26	99.99	27.26	11.20	17.51	17.37
8	21.38	21.24	99.99	17.94	10.40	18.30	17.35	21.06	22.26	99.99
9	21.29	32.94	65.91	65.44	78.33	73.16	99.99	62.69	29.99	61.18
10	58.68	72.48	67.26	99.99	55.02	109.00	187.00	178.00	198.00	212.00
11	99.99	233.00	11.73	30.87	19.86	26.59	28.47	99.99	31.29	1.13
12	0.94	0.95	0.88	0.81	99.99	0.77	10.76	11.16	11.16	13.43
13	13.43	99.99	13.43	99.99	99.99	99.99	99.99	99.99	99.99	99.99
14	99.99	99.99	99.99	99.99	99.99	99.99	99.99	99.99	99.99	99.99
15	0.00	350.00	350.00	350.00	675.00	99.99	450.00	69.00	104.00	106.00
16	109.00	138.00	99.99	122.00	75.00	104.00	106.00	111.00	136.00	99.99
17	121.00	178.00	239.00	247.00	229.00	254.00	99.99	254.00	96.00	114.00
18	121.00	104.00	121.00	99.99	121.00	99.99	171.00	174.00	161.00	192.00
19	99.99	167.00	144.00	167.00	168.00	148.00	156.00	99.99	175.00	12.00
20	12.00	13.00	10.00	16.00	99.99	16.00	170.00	212.00	220.00	200.00
21	99.99	99.99	218.00	0.27	0.29	0.29	0.27	99.99	99.99	0.26
22	12.28	24.86	26.18	24.96	35.05	99.99	30.99	99.99	17.78	18.44
23	17.55	25.12	99.99	20.37	10.80	17.37	17.81	16.43	21.22	99.99
24	21.18	33.16	72.08	75.93	67.39	99.99	99.99	80.57	31.67	63.94
25	67.63	58.86	99.99	99.99	69.15	112.00	120.00	128.00	152.00	164.00
26	99.99	169.00	15.52	13.98	14.91	17.71	22.09	99.99	19.65	1.18
27	1.29	1.21	0.91	0.85	99.99	0.94	13.86	11.65	11.65	11.65
28	13.47	99.99	11.63	99.99	99.99	99.99	99.99	99.99	99.99	99.99
29	99.99	99.99	99.99	99.99	99.99	99.99	99.99	99.99	99.99	99.99

PATIENT: PG

	1	2	3	4	5	6	7	8	9	0
0	0.00	300.00	300.00	525.00	425.00	99.99	675.00	100.00	[illegible]	[illegible]
1	157.00	153.00	99.99	179.00	100.00	135.00	136.00	155.00	140.00	99.99
2	172.00	136.00	168.00	154.00	186.00	163.00	99.99	187.00	87.00	84.00
3	88.00	95.00	90.00	99.99	97.00	106.00	121.00	109.00	121.00	118.00
4	99.99	120.00	106.00	114.00	117.00	124.00	116.00	99.99	127.00	0.00
5	0.00	0.00	0.00	0.00	99.99	0.00	129.00	132.00	133.00	160.00
6	135.00	99.99	155.00	0.22	0.18	0.19	0.20	0.18	99.99	0.18
7	14.01	22.34	20.94	29.20	24.94	99.99	33.47	10.92	16.09	14.82
8	19.31	18.05	99.99	21.48	10.60	15.39	15.91	19.22	17.17	99.99
9	21.84	30.82	40.22	39.79	58.40	44.89	99.99	60.25	29.23	31.60
10	34.37	50.24	37.18	99.99	49.94	115.00	250.00	192.00	306.00	238.00
11	99.99	322.00	10.41	26.55	20.39	30.11	23.42	99.99	99.99	0.98
12	0.46	0.61	0.41	0.49	99.99	0.39	9.05	10.62	10.62	9.84
13	9.84	99.99	99.99	99.99	99.99	99.99	99.99	99.99	99.99	99.99
14	99.99	99.99	99.99	99.99	99.99	99.99	99.99	99.99	99.99	99.99
15	0.00	450.00	450.00	575.00	675.00	99.99	925.00	69.00	112.00	112.00
16	134.00	147.00	99.99	166.00	68.00	111.00	112.00	130.00	147.00	99.99
17	165.00	145.00	164.00	158.00	181.00	177.00	99.99	194.00	87.00	77.00
18	78.00	89.00	92.00	99.99	102.00	105.00	109.00	109.00	129.00	133.00
19	99.99	149.00	109.00	118.00	119.00	122.00	133.00	99.99	139.00	2.00
20	2.00	6.00	5.00	6.00	99.99	9.00	135.00	127.00	119.00	150.00
21	158.00	99.99	165.00	0.26	0.25	0.25	0.24	0.23	99.99	0.21
22	10.01	18.37	17.70	24.25	26.02	99.99	32.20	7.25	12.21	12.21
23	17.29	19.55	99.99	24.73	7.41	13.10	13.33	15.86	19.55	99.99
24	22.94	26.01	45.92	44.24	58.21	59.84	99.99	67.60	24.22	35.56
25	33.32	48.24	53.42	99.99	57.52	117.00	174.00	174.00	195.00	210.00
26	99.99	298.00	11.40	22.25	22.25	23.71	99.99	99.99	40.59	0.91
27	0.67	0.65	0.60	0.60	99.99	0.44	9.74	12.79	12.79	12.16
28	99.99	99.99	13.62	99.99	99.99	99.99	99.99	99.99	99.99	99.99
29	99.99	99.99	99.99	99.99	99.99	99.99	99.99	99.99	99.99	99.99

PATIENT: GB

	1	2	3	4	5	6	7	8	9	10
0	0.00	300.00	325.00	450.00	525.00	99.99	450.00	74.00	101.00	106.00
1	123.00	99.99	99.99	122.00	74.00	96.00	100.00	128.00	102.00	99.99
2	122.00	125.00	153.00	134.00	147.00	99.99	99.99	164.00	80.00	73.00
3	63.00	68.00	99.99	99.99	73.00	102.00	102.00	93.00	96.00	99.99
4	99.99	105.00	93.00	105.00	94.00	103.00	100.00	99.99	103.00	0.00
5	2.00	2.00	1.00	0.00	99.99	1.00	114.00	140.00	121.00	100.00
6	99.99	99.99	135.00	0.23	0.25	0.22	0.21	99.99	99.99	0.21
7	9.25	15.30	14.20	18.08	99.99	99.99	20.01	7.55	10.20	9.86
8	11.81	99.99	99.99	12.31	6.88	10.08	9.40	13.18	13.20	99.99
9	13.18	21.28	38.25	31.25	37.97	99.99	99.99	42.02	19.40	35.00
10	28.22	33.58	99.99	99.99	34.59	74.00	167.00	162.00	154.00	134.00
11	99.99	201.00	7.72	17.22	16.70	18.20	17.07	99.99	23.76	1.26
12	0.62	0.57	0.66	0.75	99.99	0.53	10.43	10.31	10.31	11.82
13	12.74	99.99	11.82	99.99	99.99	99.99	99.99	99.99	99.99	99.99
14	99.99	99.99	99.99	99.99	99.99	99.99	99.99	99.99	99.99	99.99
15	99.99	99.99	99.99	99.99	99.99	99.99	99.99	99.99	99.99	99.99
16	99.99	99.99	99.99	99.99	99.99	99.99	99.99	99.99	99.99	99.99
17	99.99	99.99	99.99	99.99	99.99	99.99	99.99	99.99	99.99	99.99
18	99.99	99.99	99.99	99.99	99.99	99.99	99.99	99.99	99.99	99.99
19	99.99	99.99	99.99	99.99	99.99	99.99	99.99	99.99	99.99	99.99
20	99.99	99.99	99.99	99.99	99.99	99.99	99.99	99.99	99.99	99.99
21	99.99	99.99	99.99	99.99	99.99	99.99	99.99	99.99	99.99	99.99
22	99.99	99.99	99.99	99.99	99.99	99.99	99.99	99.99	99.99	99.99
23	99.99	99.99	99.99	99.99	99.99	99.99	99.99	99.99	99.99	99.99
24	99.99	99.99	99.99	99.99	99.99	99.99	99.99	99.99	99.99	99.99
25	99.99	99.99	99.99	99.99	99.99	99.99	99.99	99.99	99.99	99.99
26	99.99	99.99	99.99	99.99	99.99	99.99	99.99	99.99	99.99	99.99
27	99.99	99.99	99.99	99.99	99.99	99.99	99.99	99.99	99.99	99.99
28	99.99	99.99	99.99	99.99	99.99	99.99	99.99	99.99	99.99	99.99
29	99.99	99.99	99.99	99.99	99.99	99.99	99.99	99.99	99.99	99.99

PATIENT: YL

	1	2	3	4	5	6	7	8	9	
0	0.00	225.00	175.00	275.00	175.00	450.00	450.00	84.00	103.00	[illegible]
1	147.00	116.00	148.00	99.99	86.00	100.00	101.00	115.00	120.00	141.00
2	147.00	174.00	182.00	167.00	173.00	180.00	184.00	99.99	106.00	104.00
3	102.00	105.00	102.00	111.00	99.99	134.00	142.00	132.00	135.00	142.00
4	142.00	99.99	132.00	139.00	141.00	135.00	132.00	147.00	146.00	4.00
5	6.00	6.00	5.00	4.00	3.00	5.00	156.00	172.00	152.00	165.00
6	165.00	165.00	99.99	0.25	0.23	0.23	0.22	0.21	0.21	99.99
7	14.62	18.56	16.87	20.24	20.88	27.22	99.99	11.26	14.48	13.33
8	15.80	16.47	21.02	99.99	11.35	13.90	14.24	15.53	15.84	20.73
9	21.46	36.54	42.70	38.79	44.53	43.85	57.19	99.99	23.76	40.25
10	35.31	42.47	40.19	51.28	99.99	139.00	139.00	145.00	147.00	152.00
11	195.00	211.00	20.36	21.82	22.77	23.06	23.85	31.55	34.14	0.92
12	0.96	0.93	0.88	0.84	0.74	0.67	14.65	15.70	15.70	15.69
13	15.69	16.18	16.18	99.99	99.99	99.99	99.99	99.99	99.99	99.99
14	99.99	99.99	99.99	99.99	99.99	99.99	99.99	99.99	99.99	99.99
15	0.00	275.00	275.00	450.00	99.99	99.99	450.00	82.00	106.00	105.00
16	119.00	99.99	99.99	128.00	78.00	93.00	106.00	113.00	99.99	99.99
17	128.00	151.00	176.00	167.00	183.00	99.99	99.99	196.00	100.00	103.00
18	100.00	100.00	99.99	99.99	111.00	128.00	139.00	135.00	153.00	99.99
19	99.99	154.00	125.00	127.00	136.00	142.00	99.99	99.99	151.00	8.00
20	5.00	.0.00	8.00	99.99	99.99	7.00	141.00	157.00	162.00	174.00
21	99.99	99.99	188.00	0.23	0.25	0.25	0.24	99.99	99.99	0.23
22	12.38	18.66	17.54	21.78	99.99	99.99	25.09	10.50	14.73	14.13
23	13.21	99.99	99.99	19.71	9.75	11.81	14.42	16.05	99.99	99.99
24	19.33	28.48	46.64	43.84	52.26	99.99	99.99	57.70	26.59	41.61
25	42.53	49.69	99.99	99.99	55.35	97.00	107.00	127.00	144.00	99.99
26	99.99	158.00	11.85	15.64	18.57	22.39	99.99	99.99	25.47	1.21
27	1.14	0.99	0.93	99.99	99.99	0.91	12.22	14.62	14.62	15.55
28	99.99	99.99	16.12	99.99	99.99	99.99	99.99	99.99	99.99	99.99
29	99.99	99.99	99.99	99.99	99.99	99.99	99.99	99.99	99.99	99.99

PATIENT: HD

	1	2	3	4	5	6	7	8	9	10
0	0.00	300.00	375.00	99.99	99.99	99.99	375.00	71.00	123.00	139.00
1	99.99	99.99	99.99	132.00	73.00	119.00	132.00	99.99	99.99	99.99
2	131.00	153.00	171.00	170.00	99.99	99.99	99.99	160.00	91.00	96.00
3	98.00	99.99	99.99	99.99	91.00	117.00	129.00	127.00	99.99	99.99
4	99.99	124.00	120.00	124.00	126.00	99.99	99.99	99.99	122.00	3.00
5	4.00	3.00	99.99	99.99	99.99	4.00	142.00	151.00	147.00	99.99
6	99.99	99.99	140.00	0.26	0.22	0.21	99.99	99.99	99.99	0.21
7	10.86	21.03	23.63	99.99	99.99	99.99	21.12	8.31	15.87	17.65
8	99.99	99.99	99.99	16.37	8.76	14.76	16.63	99.99	99.99	99.99
9	15.98	28.24	46.27	49.62	99.99	99.99	99.99	44.35	26.21	40.86
10	42.91	99.99	99.99	99.99	38.81	87.00	138.00	140.00	99.99	99.99
11	99.99	164.00	7.92	13.98	16.24	99.99	99.99	99.99	18.65	1.34
12	0.87	0.88	99.99	99.99	99.99	0.72	9.10	10.13	11.60	99.99
13	99.99	99.99	11.37	99.99	99.99	99.99	99.99	99.99	99.99	99.99
14	99.99	99.99	99.99	99.99	99.99	99.99	99.99	99.99	99.99	99.99
15	0.00	300.00	375.00	375.00	99.99	99.99	375.00	68.00	101.00	108.00
16	108.00	99.99	99.99	134.00	68.00	93.00	100.00	106.00	99.99	99.99
17	130.00	132.00	151.00	158.00	160.00	99.99	99.99	175.00	82.00	85.00
18	85.00	87.00	99.99	99.99	98.00	108.00	115.00	122.00	123.00	99.99
19	99.99	135.00	103.00	117.00	122.00	123.00	99.99	99.99	142.00	3.00
20	4.00	6.00	6.00	99.99	99.99	13.00	122.00	128.00	148.00	142.00
21	99.99	99.99	165.00	0.27	0.26	0.26	0.24	99.99	99.99	0.23
22	8.98	15.25	17.06	17.28	99.99	99.99	23.45	7.34	11.62	13.18
23	13.28	99.99	99.99	18.09	7.00	10.88	12.20	13.04	99.99	99.99
24	18.46	24.24	39.65	44.37	41.47	99.99	99.99	53.94	22.40	33.61
25	41.56	36.81	99.99	99.99	50.85	78.00	117.00	167.00	102.00	99.99
26	99.99	192.00	8.21	13.34	20.66	12.62	99.99	99.99	24.02	1.28
27	0.97	0.69	1.15	99.99	99.99	0.67	10.53	11.40	12.37	12.37
28	99.99	99.99	12.51	99.99	99.99	99.99	99.99	99.99	99.99	99.99
29	99.99	99.99	99.99	99.99	99.99	99.99	99.99	99.99	99.99	99.99

PATIENT LP	1	2	3	4	5	6	7	8	9	10
0	0.00	450.00	375.00	450.00	475.00	99.99	525.00	71.00	112.00	114.00
1	142.00	145.00	99.99	138.00	71.00	114.00	113.00	135.00	142.00	99.99
2	131.00	125.00	173.00	124.00	152.00	156.00	99.99	181.00	69.00	69.00
3	84.00	73.00	70.00	99.99	78.00	85.00	113.00	83.00	101.00	101.00
4	99.99	113.00	87.00	115.00	88.00	101.00	100.00	99.99	109.00	0.00
5	3.00	2.00	4.00	3.00	99.99	4.00	103.00	148.00	110.00	131.00
6	121.00	99.99	148.00	0.25	0.24	0.22	0.20	0.19	99.99	0.20
7	8.88	19.38	14.14	21.58	22.52	99.99	24.98	6.04	12.66	9.46
8	14.34	14.65	99.99	15.59	6.19	13.11	9.94	13.64	14.20	99.99
9	14.28	22.19	46.50	31.10	43.17	42.98	99.99	49.96	18.28	39.73
10	27.59	37.20	33.34	99.99	40.85	79.00	140.00	127.00	126.00	146.00
11	99.99	177.00	8.26	16.53	15.00	16.87	18.38	99.99	23.70	1.10
12	0.80	0.68	0.77	0.66	99.99	0.59	10.45	11.81	11.81	13.39
13	12.59	99.99	13.39	99.99	99.99	99.99	99.99	99.99	99.99	99.99
14	99.99	99.99	99.99	99.99	99.99	99.99	99.99	99.99	99.99	99.99
15	0.00	475.00	475.00	575.00	575.00	99.99	650.00	66.00	115.00	137.00
16	143.00	142.00	99.99	159.00	63.00	116.00	138.00	139.00	143.00	99.99
17	165.00	119.00	177.00	168.00	172.00	166.00	99.99	152.00	68.00	78.00
18	77.00	78.00	77.00	99.99	75.00	93.00	112.00	104.00	114.00	111.00
19	99.99	113.00	92.00	112.00	107.00	109.00	107.00	99.99	117.00	99.99
20	0.00	1.00	0.00	1.00	99.99	4.00	106.00	145.00	143.00	148.00
21	133.00	99.99	138.00	0.25	0.23	0.19	0.18	0.19	99.99	0.19
22	7.85	20.36	23.02	24.60	23.57	99.99	24.17	6.14	12.88	14.25
23	16.30	15.76	99.99	17.97	5.80	12.99	14.77	15.15	15.30	99.99
24	19.31	19.64	46.82	43.73	44.27	44.79	99.99	45.92	17.49	38.35
25	37.22	38.10	35.88	99.99	41.69	88.00	161.00	159.00	197.00	225.00
26	99.99	258.00	9.33	20.04	19.80	20.59	23.51	99.99	29.82	1.05
27	0.70	0.67	0.55	0.47	99.99	0.44	10.60	12.45	12.45	10.45
28	10.45	99.99	11.56	99.99	99.99	99.99	99.99	99.99	99.99	99.99
29	99.99	99.99	99.99	99.99	99.99	99.99	99.99	99.99	99.99	99.99